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(54) Title: MAIZE CELLULOSE SYNTHASES AND USES THEREOF

(57) Abstract

The invention provides isolated cellulose synthase nucleic acids and their encoded proteins. The present invention provides methods and compositions relating to altering cellulose synthase concentration and/or composition of plants. The invention further provides recombinant expression cassettes, host cells, and transgenic plants.

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Maize Cellulose Synthases and Uses Thereof

TECHNICAL FIELD

The present invention relates generally to plant molecular biology. More specifically, it relates to nucleic acids and methods for modulating their expression in plants.

BACKGROUND OF THE INVENTION

Polysaccharides constitute the bulk of the plant cell walls and have been traditionally classified into three categories: cellulose, hemicellulose, and pectin. Fry, S. C. (1988), *The growing plant cell wall: Chemical and metabolic analysis*. New York: Longman Scientific & Technical. Whereas cellulose is made at the plasma membrane and directly laid down into the cell wall, hemicellulosic and pectic polymers are first made in the Golgi apparatus and then exported to the cell wall by exocytosis. Ray, P. M., et al., (1976), *Ber. Deutsch. Bot. Ges. Bd.* 89, 121-146. The variety of chemical linkages in the pectic and hemicellulosic polysaccharides indicates that there must be tens of polysaccharide synthases in the Golgi apparatus. Darvill et al., (1980). The primary cell walls of flowering plants. In *The Plant Cell* (N. E. Tolbert, ed.), *Vol. 1 in Series: The biochemistry of plants: A comprehensive treatise*, eds. P.K. Stumpf and E.E. Conn (New York: Academic Press), pp. 91-162.

Cellulose, by virtue of its ability to form semicrystalline microfibrils, has a very high tensile strength which approaches that of some metals. Niklas, K. J. (1992). *Plant Biomechanics: An engineering approach to plant form and function*, The University of Chicago Press, pp. 607. Bending strength of the culm of normal and brittle-culm mutants of barley has been found to be directly correlated with the concentration of cellulose in the cell wall. Kokubo, et al., (1989), *Plant Physiology* 91, 876-882; Kokubo, et al., (1991) *Plant Physiology* 97, 509-514.

Even though sugar and polysaccharide compositions of the plant cell walls have been well characterized, very limited progress has been made toward identification of the enzymes involved in polysaccharides formation, the reason being their labile nature and recalcitrance to solubilization by available detergents. Sporadic claims for the identification of cellulose synthase from plant sources have been made over the years. Callaghan, T., and Benziman, M. (1984), *Nature* 311, 165-167; Okuda, et al., (1993),

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Plant Physiol. 101, 1131-1142. However, these claims have been met with skepticism. Callaghan, T., and Benziman, M. (1985), *Nature* 314, 383-384; Delmer, *et al.*, (1993), Plant Physiol. 103, 307-308. It was only recently that a putative gene for plant cellulose synthase (CelA) was cloned from the developing cotton fibers based on homology to the bacterial gene. Pear, *et al.*, *Proc. Natl. Acad. Sci. (USA)* 93, 12637-12642; Saxena, *et al.*, (1990), *Plant Molecular Biology* 15, 673-684; see also, WO 9818949.

As brittle snap is a major problem in corn breeding, what is needed in the art are compositions and methods for manipulating cellulose concentration in the cell wall and thereby altering plant stalk quality for improved standability or silage. The present invention provides these and other advantages.

SUMMARY OF THE INVENTION

Generally, it is the object of the present invention to provide nucleic acids and proteins relating to cellulose synthases. It is an object of the present invention to provide: 1) nucleic acids and proteins relating to maize cellulose synthases; 2) transgenic plants comprising the nucleic acids of the present invention; 3) methods for modulating, in a transgenic plant, the expression of the nucleic acids of the present invention.

Therefore, in one aspect, the present invention relates to an isolated nucleic acid comprising a member selected from the group consisting of (a) a polynucleotide having a specified sequence identity to a polynucleotide encoding a polypeptide of the present invention; (b) a polynucleotide which is complementary to the polynucleotide of (a); and (c) a polynucleotide comprising a specified number of contiguous nucleotides from a polynucleotide of (a) or (b). The isolated nucleic acid can be DNA or RNA.

In another aspect, the present invention relates to recombinant expression cassettes, comprising a nucleic acid of the present invention operably linked to a promoter. In some embodiments, the nucleic acid is operably linked in antisense orientation to the promoter.

In another aspect, the present invention is directed to a host cell transfected with the recombinant expression cassette.

In a further aspect, the present invention relates to an isolated protein comprising a polypeptide having a specified number of contiguous amino acids encoded by an isolated nucleic acid of the present invention.

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In another aspect, the present invention relates to an isolated nucleic acid comprising a polynucleotide of specified length which selectively hybridizes under stringent conditions to a polynucleotide of the present invention, or a complement thereof. In some embodiments, the isolated nucleic acid is operably linked to a promoter.

5 In yet another aspect, the present invention relates to an isolated nucleic acid comprising a polynucleotide, the polynucleotide having a specified sequence identity to an identical length of a nucleic acid of the present invention or a complement thereof.

10 In another aspect, the present invention relates to an isolated nucleic acid comprising a polynucleotide having a sequence of a nucleic acid amplified from a *Zea mays* nucleic acid library using at least two primers or their complements, one of which selectively hybridizes under stringent conditions to a locus of the nucleic acid comprising the 5' terminal coding region and the other primer selectively hybridizing, under stringent conditions, to a locus of the nucleic acid comprising the 3' terminal coding 15 region, and wherein both primers selectively hybridize within the coding region. In some embodiments, the nucleic acid library is a cDNA library.

20 In another aspect, the present invention relates to a recombinant expression cassette comprising a nucleic acid, wherein the nucleic acid is operably linked to a promoter. In some embodiments, the present invention relates to a host cell transfected with this recombinant expression cassette. In some embodiments, the present invention relates to a protein of the present invention which is produced from this host cell.

25 In a further aspect, the present invention relates to a heterologous promoter operably linked to a non-isolated polynucleotide of the present invention, wherein the polypeptide is encoded by a nucleic acid amplified from a nucleic acid library.

30 In yet another aspect, the present invention relates to a transgenic plant comprising a recombinant expression cassette comprising a plant promoter operably linked to any of the isolated nucleic acids of the present invention. In some embodiments, the transgenic plant is *Zea mays*. The present invention also provides transgenic seed from the transgenic plant.

35 In a further aspect, the present invention relates to a method of modulating expression of the genes encoding the proteins of the present invention in a plant cell capable of plant regeneration, comprising the steps of (a) transforming a plant cell with a recombinant expression cassette comprising a polynucleotide of the present invention

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operably linked to a promoter; (b) growing the plant cell under plant growing conditions; and (c) inducing expression of the polynucleotide for a time sufficient to modulate expression of the genes in the plant. In some embodiments, the plant is maize. Expression of the genes encoding the proteins of the present invention can be increased 5 or decreased relative to a non-transformed control plant.

Definitions

Units, prefixes, and symbols may be denoted in their SI accepted form. Unless otherwise indicated, nucleic acids are written left to right in 5' to 3' orientation; amino 10 acid sequences are written left to right in amino to carboxy orientation, respectively. Numeric ranges are inclusive of the numbers defining the range and include each integer within the defined range. Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be 15 referred to by their commonly accepted single-letter codes. Unless otherwise provided for, software, electrical, and electronics terms as used herein are as defined in The New IEEE Standard Dictionary of Electrical and electronics Terms (5th edition, 1993). The terms defined below are more fully defined by reference to the specification as a whole.

By "amplified" is meant the construction of multiple copies of a nucleic acid 20 sequence or multiple copies complementary to the nucleic acid sequence using at least one of the nucleic acid sequences as a template. Amplification systems include the polymerase chain reaction (PCR) system, ligase chain reaction (LCR) system, nucleic acid sequence based amplification (NASBA, Cangene, Mississauga, Ontario), Q-Beta Replicase systems, transcription-based amplification system (TAS), and strand 25 displacement amplification (SDA). See, e.g., *Diagnostic Molecular Microbiology: Principles and Applications*, D. H. Persing *et al.*, Ed., American Society for Microbiology, Washington, D.C. (1993). The product of amplification is termed an amplicon.

The term "antibody" includes reference to antigen binding forms of antibodies 30 (e.g., Fab, F(ab)₂). The term "antibody" frequently refers to a polypeptide substantially encoded by an immunoglobulin gene or immunoglobulin genes, or fragments thereof which specifically bind and recognize an analyte (antigen). However, while various antibody fragments can be defined in terms of the digestion of an intact antibody, one of

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skill will appreciate that such fragments may be synthesized *de novo* either chemically or by utilizing recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments such as single chain Fv, chimeric antibodies (i.e., comprising constant and variable regions from different species), humanized antibodies
5 (i.e., comprising a complementarity determining region (CDR) from a non-human source) and heteroconjugate antibodies (e.g., bispecific antibodies).

- The term "antigen" includes reference to a substance to which an antibody can be generated and/or to which the antibody is specifically immunoreactive. The specific immunoreactive sites within the antigen are known as epitopes or antigenic determinants.
10 These epitopes can be a linear array of monomers in a polymeric composition - such as amino acids in a protein - or consist of or comprise a more complex secondary or tertiary structure. Those of skill will recognize that all immunogens (i.e., substances capable of eliciting an immune response) are antigens; however some antigens, such as haptens, are not immunogens but may be made immunogenic by coupling to a carrier molecule. An
15 antibody immunologically reactive with a particular antigen can be generated *in vivo* or by recombinant methods such as selection of libraries of recombinant antibodies in phage or similar vectors. See, e.g., Huse *et al.*, *Science* 246: 1275-1281 (1989); and Ward, *et al.*, *Nature* 341: 544-546 (1989); and Vaughan *et al.*, *Nature Biotech.* 14: 309-314 (1996).
20 As used herein, "antisense orientation" includes reference to a duplex polynucleotide sequence which is operably linked to a promoter in an orientation where the antisense strand is transcribed. The antisense strand is sufficiently complementary to an endogenous transcription product such that translation of the endogenous transcription product is often inhibited.
25 As used herein, "chromosomal region" includes reference to a length of a chromosome which may be measured by reference to the linear segment of DNA which it comprises. The chromosomal region can be defined by reference to two unique DNA sequences, i.e., markers.

The term "conservatively modified variants" applies to both amino acid and
30 nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or conservatively modified variants of the amino acid sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein.

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- For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations" and represent one species of conservatively modified variation. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid.
- One of ordinary skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine; and UGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule.
- Accordingly, each silent variation of a nucleic acid which encodes a polypeptide of the present invention is implicit in each described polypeptide sequence and incorporated herein by reference.
- As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Thus, any number of amino acid residues selected from the group of integers consisting of from 1 to 15 can be so altered. Thus, for example, 1, 2, 3, 4, 5, 7, or 10 alterations can be made. Conservatively modified variants typically provide similar biological activity as the unmodified polypeptide sequence from which they are derived. For example, substrate specificity, enzyme activity, or ligand/receptor binding is generally at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the native protein for its native substrate. Conservative substitution tables providing functionally similar amino acids are well known in the art.

The following six groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Serine (S), Threonine (T);
- 2) Aspartic acid (D), Glutamic acid (E);
- 30 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

See also, Creighton (1984) Proteins W.H. Freeman and Company.

By "encoding" or "encoded", with respect to a specified nucleic acid, is meant comprising the information for translation into the specified protein. A nucleic acid encoding a protein may comprise non-translated sequences (e.g., introns) within 5 translated regions of the nucleic acid, or may lack such intervening non-translated sequences (e.g., as in cDNA). The information by which a protein is encoded is specified by the use of codons. Typically, the amino acid sequence is encoded by the nucleic acid using the "universal" genetic code. However, variants of the universal code, such as are present in some plant, animal, and fungal mitochondria, the bacterium 10 *Mycoplasma capricolum* (*Proc. Natl. Acad. Sci. (USA)*, 82: 2306-2309 (1985)), or the ciliate *Macronucleus*, may be used when the nucleic acid is expressed using these organisms.

When the nucleic acid is prepared or altered synthetically, advantage can be taken of known codon preferences of the intended host where the nucleic acid is to be 15 expressed. For example, although nucleic acid sequences of the present invention may be expressed in both monocotyledonous and dicotyledonous plant species, sequences can be modified to account for the specific codon preferences and GC content preferences of monocotyledons or dicotyledons as these preferences have been shown to differ (Murray *et al.* *Nucl. Acids Res.* 17: 477-498 (1989)). Thus, the maize preferred codon for a 20 particular amino acid may be derived from known gene sequences from maize. Maize codon usage for 28 genes from maize plants are listed in Table 4 of Murray *et al.*, above.

As used herein "full-length sequence" in reference to a specified polynucleotide or its encoded protein means having the entire amino acid sequence of, a native (non-synthetic), endogenous, catalytically active form of the specified protein. Methods to determine whether a sequence is full-length are well known in the art including such exemplary techniques as northern or western blots, primer extension, S1 protection, and ribonuclease protection. See, e.g., *Plant Molecular Biology: A Laboratory Manual*, Clark, Ed., Springer-Verlag, Berlin (1997). Comparison to known full-length 25 homologous (orthologous and/or paralogous) sequences can also be used to identify full-length sequences of the present invention. Additionally, consensus sequences typically present at the 5' and 3' untranslated regions of mRNA aid in the identification of a 30 polynucleotide as full-length. For example, the consensus sequence ANNNNAUGG,

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where the underlined codon represents the N-terminal methionine, aids in determining whether the polynucleotide has a complete 5' end. Consensus sequences at the 3' end, such as polyadenylation sequences, aid in determining whether the polynucleotide has a complete 3' end.

- 5 The term "gene activity" refers to one or more steps involved in gene expression, including transcription, translation, and the functioning of the protein encoded by the gene.

As used herein, "heterologous" in reference to a nucleic acid is a nucleic acid that originates from a foreign species, or, if from the same species, is substantially modified
10 from its native form in composition and/or genomic locus by deliberate human intervention. For example, a promoter operably linked to a heterologous structural gene is from a species different from that from which the structural gene was derived, or, if from the same species, one or both are substantially modified from their original form.
A heterologous protein may originate from a foreign species or, if from the same
15 species, is substantially modified from its original form by deliberate human intervention.

By "host cell" is meant a cell which contains a vector and supports the replication and/or expression of the expression vector. Host cells may be prokaryotic cells such as *E. coli*, or eukaryotic cells such as yeast, insect, amphibian, or mammalian cells.
20 Preferably, host cells are monocotyledonous or dicotyledonous plant cells. A particularly preferred monocotyledonous host cell is a maize host cell.

The term "hybridization complex" includes reference to a duplex nucleic acid structure formed by two single-stranded nucleic acid sequences selectively hybridized with each other.

- 25 By "immunologically reactive conditions" or "immunoreactive conditions" is meant conditions which allow an antibody, generated to a particular epitope, to bind to that epitope to a detectably greater degree (e.g., at least 2-fold over background) than the antibody binds to substantially all other epitopes in a reaction mixture comprising the particular epitope. Immunologically reactive conditions are dependent upon the format
30 of the antibody binding reaction and typically are those utilized in immunoassay protocols. See Harlow and Lane, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, New York (1988), for a description of immunoassay formats and conditions.

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The term "introduced" in the context of inserting a nucleic acid into a cell, means "transfection" or "transformation" or "transduction" and includes reference to the incorporation of a nucleic acid into a eukaryotic or prokaryotic cell where the nucleic acid may be incorporated into the genome of the cell (e.g., chromosome, plasmid, 5 plastid or mitochondrial DNA), converted into an autonomous replicon, or transiently expressed (e.g., transfected mRNA).

The terms "isolated" refers to material, such as a nucleic acid or a protein, which is: (1) substantially or essentially free from components which normally accompany or interact with it as found in its naturally occurring environment. The isolated material 10 optionally comprises material not found with the material in its natural environment; or (2) if the material is in its natural environment, the material has been synthetically (non-naturally) altered by deliberate human intervention to a composition and/or placed at a locus in the cell (e.g., genome or subcellular organelle) not native to a material found in that environment. The alteration to yield the synthetic material can be performed on the 15 material within or removed from its natural state. For example, a naturally occurring nucleic acid becomes an isolated nucleic acid if it is altered, or if it is transcribed from DNA which has been altered, by non-natural, synthetic (i.e., "man-made") methods performed within the cell from which it originates. See, e.g., Compounds and Methods for Site Directed Mutagenesis in Eukaryotic Cells, Kmiec, U.S. Patent No. 5,565,350; 20 *In Vivo* Homologous Sequence Targeting in Eukaryotic Cells; Zarling *et al.*, PCT/US93/03868. Likewise, a naturally occurring nucleic acid (e.g., a promoter) becomes isolated if it is introduced by non-naturally occurring means to a locus of the genome not native to that nucleic acid. Nucleic acids which are "isolated" as defined herein, are also referred to as "heterologous" nucleic acids.

25 Unless otherwise stated, the term "cellulose synthase nucleic acid" is a nucleic acid of the present invention and means a nucleic acid comprising a polynucleotide of the present invention (a "cellulose synthase polynucleotide") encoding a cellulose synthase polypeptide. A "cellulose synthase gene" is a gene of the present invention and refers to a non-heterologous genomic form of a full-length cellulose synthase polynucleotide.

30 As used herein, "localized within the chromosomal region defined by and including" with respect to particular markers includes reference to a contiguous length of a chromosome delimited by and including the stated markers.

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As used herein, "marker" includes reference to a locus on a chromosome that serves to identify a unique position on the chromosome. A "polymorphic marker" includes reference to a marker which appears in multiple forms (alleles) such that different forms of the marker, when they are present in a homologous pair, allow 5 transmission of each of the chromosomes in that pair to be followed. A genotype may be defined by use of one or a plurality of markers.

As used herein, "nucleic acid" includes reference to a deoxyribonucleotide or ribonucleotide polymer in either single- or double-stranded form, and unless otherwise limited, encompasses known analogues having the essential nature of natural nucleotides 10 in that they hybridize to single-stranded nucleic acids in a manner similar to naturally occurring nucleotides (e.g., peptide nucleic acids).

By "nucleic acid library" is meant a collection of isolated DNA or RNA molecules which comprise and substantially represent the entire transcribed fraction of a genome of a specified organism. Construction of exemplary nucleic acid libraries, such 15 as genomic and cDNA libraries, is taught in standard molecular biology references such as Berger and Kimmel, *Guide to Molecular Cloning Techniques, Methods in Enzymology*, Vol. 152, Academic Press, Inc., San Diego, CA (Berger); Sambrook *et al.*, *Molecular Cloning - A Laboratory Manual*, 2nd ed., Vol. 1-3 (1989); and *Current Protocols in Molecular Biology*, F.M. Ausubel *et al.*, Eds., Current Protocols, a joint 20 venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc. (1994 Supplement).

As used herein "operably linked" includes reference to a functional linkage between a promoter and a second sequence, wherein the promoter sequence initiates and mediates transcription of the DNA sequence corresponding to the second sequence. 25 Generally, operably linked means that the nucleic acid sequences being linked are contiguous and, where necessary to join two protein coding regions, contiguous and in the same reading frame.

As used herein, the term "plant" includes reference to whole plants, plant parts or organs (e.g., leaves, stems, roots, etc.), plant cells, seeds and progeny of same. Plant 30 cell, as used herein includes, without limitation, cells obtained from or found in: seeds, suspension cultures, embryos, meristematic regions, callus tissue, leaves, roots, shoots, gametophytes, sporophytes, pollen, and microspores. Plant cells can also be understood to include modified cells, such as protoplasts, obtained from the aforementioned tissues.

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The class of plants which can be used in the methods of the invention is generally as broad as the class of higher plants amenable to transformation techniques, including both monocotyledonous and dicotyledonous plants. Particularly preferred plants include maize, soybean, sunflower, sorghum, canola, wheat, alfalfa, cotton, rice, barley and millet.

5

As used herein, "polynucleotide" includes reference to a deoxyribopolynucleotide, ribopolynucleotide, or analogs thereof that have the essential nature of a natural ribonucleotide in that they hybridize, under stringent hybridization conditions, to substantially the same nucleotide sequence as naturally occurring 10 nucleotides and/or allow translation into the same amino acid(s) as the naturally occurring nucleotide(s). A polynucleotide can be full-length or a subsequence of a native or heterologous structural or regulatory gene. Unless otherwise indicated, the term includes reference to the specified sequence as well as the complementary sequence thereof. Thus, DNAs or RNAs with backbones modified for stability or for other reasons 15 are "polynucleotides" as that term is intended herein. Moreover, DNAs or RNAs comprising unusual bases, such as inosine, or modified bases, such as tritylated bases, to name just two examples, are polynucleotides as the term is used herein. It will be appreciated that a great variety of modifications have been made to DNA and RNA that serve many useful purposes known to those of skill in the art. The term polynucleotide as 20 it is employed herein embraces such chemically, enzymatically or metabolically modified forms of polynucleotides, as well as the chemical forms of DNA and RNA characteristic of viruses and cells, including *among other things*, simple and complex cells.

The terms "polypeptide", "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in 25 which one or more amino acid residue is an artificial chemical analogue of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers. The essential nature of such analogues of naturally occurring amino acids is that, when incorporated into a protein, that protein is specifically reactive to antibodies elicited to the same protein but consisting entirely of naturally occurring 30 amino acids. The terms "polypeptide", "peptide" and "protein" are also inclusive of modifications including, but not limited to, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation. Exemplary modifications are described in most basic texts, such as, *Proteins - Structure*

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and Molecular Properties, 2nd ed., T. E. Creighton, W. H. Freeman and Company, New York (1993). Many detailed reviews are available on this subject, such as, for example, those provided by Wold, F., Post-translational Protein Modifications: Perspectives and Prospects, pp. 1-12 in *Posttranslational Covalent Modification of Proteins*, B. C. Johnson, 5 Ed., Academic Press, New York (1983); Seifter *et al.*, *Meth. Enzymol.* 182: 626-646 (1990) and Rattan *et al.*, *Protein Synthesis: Posttranslational Modifications and Aging*, *Ann. N.Y. Acad. Sci.* 663: 48-62 (1992). It will be appreciated, as is well known and as noted above, that polypeptides are not always entirely linear. For instance, polypeptides may be branched as a result of ubiquitination, and they may be circular, with or without 10 branching, generally as a result of posttranslation events, including natural processing event and events brought about by human manipulation which do not occur naturally. Circular, branched and branched circular polypeptides may be synthesized by non-translation natural process and by entirely synthetic methods, as well. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side- 15 chains and the amino or carboxyl termini. In fact, blockage of the amino or carboxyl group in a polypeptide, or both, by a covalent modification, is common in naturally occurring and synthetic polypeptides and such modifications may be present in polypeptides of the present invention, as well. For instance, the amino terminal residue of polypeptides made in *E. coli* or other cells, prior to proteolytic processing, almost 20 invariably will be N-formylmethionine. During post-translational modification of the peptide, a methionine residue at the NH₂-terminus may be deleted. Accordingly, this invention contemplates the use of both the methionine-containing and the methionine-less amino terminal variants of the protein of the invention. In general, as used herein, the term polypeptide encompasses all such modifications, particularly those that are present in 25 polypeptides synthesized by expressing a polynucleotide in a host cell.

As used herein "promoter" includes reference to a region of DNA upstream from the start of transcription and involved in recognition and binding of RNA polymerase and other proteins to initiate transcription. A "plant promoter" is a promoter capable of initiating transcription in plant cells. Exemplary plant promoters include, but are not 30 limited to, those that are obtained from plants, plant viruses, and bacteria which comprise genes expressed in plant cells such *Agrobacterium* or *Rhizobium*. Examples of promoters under developmental control include promoters that preferentially initiate transcription in certain tissues, such as leaves, roots, or seeds. Such promoters are

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referred to as "tissue preferred". Promoters which initiate transcription only in certain tissue are referred to as "tissue specific". A "cell type" specific promoter primarily drives expression in certain cell types in one or more organs, for example, vascular cells in roots or leaves. An "inducible" promoter is a promoter which is under environmental control. Examples of environmental conditions that may effect transcription by inducible promoters include anaerobic conditions or the presence of light. Tissue specific, tissue preferred, cell type specific, and inducible promoters constitute the class of "non-constitutive" promoters. A "constitutive" promoter is a promoter which is active under most environmental conditions.

10 The term "cellulose synthase polypeptide" is a polypeptide of the present invention and refers to one or more amino acid sequences, in glycosylated or non-glycosylated form. The term is also inclusive of fragments, variants, homologs, alleles or precursors (e.g., preproproteins or proproteins) thereof. A "cellulose synthase protein" is a protein of the present invention and comprises a cellulose synthase polypeptide.

15 As used herein "recombinant" includes reference to a cell or vector, that has been modified by the introduction of a heterologous nucleic acid or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found in identical form within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under-expressed or not expressed at all as a result of deliberate human intervention. The term "recombinant" as used herein does not encompass the alteration of the cell or vector by naturally occurring events (e.g., spontaneous mutation, natural transformation/transduction/transposition) such as those occurring without deliberate human intervention.

20 As used herein, a "recombinant expression cassette" is a nucleic acid construct, generated recombinantly or synthetically, with a series of specified nucleic acid elements which permit transcription of a particular nucleic acid in a host cell. The recombinant expression cassette can be incorporated into a plasmid, chromosome, mitochondrial DNA, plastid DNA, virus, or nucleic acid fragment. Typically, the recombinant expression cassette portion of an expression vector includes, among other sequences, a nucleic acid to be transcribed, and a promoter.

25 The term "residue" or "amino acid residue" or "amino acid" are used interchangeably herein to refer to an amino acid that is incorporated into a protein,

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polypeptide, or peptide (collectively "protein"). The amino acid may be a naturally occurring amino acid and, unless otherwise limited, may encompass known analogs of natural amino acids that can function in a similar manner as naturally occurring amino acids.

5 The term "selectively hybridizes" includes reference to hybridization, under stringent hybridization conditions, of a nucleic acid sequence to a specified nucleic acid target sequence to a detectably greater degree (e.g., at least 2-fold over background) than its hybridization to non-target nucleic acid sequences and to the substantial exclusion of non-target nucleic acids. Selectively hybridizing sequences typically have about at least 10 80% sequence identity, preferably 90% sequence identity, and most preferably 100% sequence identity (i.e., complementary) with each other.

15 The term "specifically reactive", includes reference to a binding reaction between an antibody and a protein having an epitope recognized by the antigen binding site of the antibody. This binding reaction is determinative of the presence of a protein having the recognized epitope amongst the presence of a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to an analyte having the recognized epitope to a substantially greater degree (e.g., at least 2-fold over background) than to substantially all other analytes lacking the epitope which are present in the sample.

20 The terms "stringent conditions" or "stringent hybridization conditions" includes reference to conditions under which a probe will hybridize to its target sequence, to a detectably greater degree than other sequences (e.g., at least 2-fold over background). Stringent conditions are sequence-dependent and will be different in different circumstances. By controlling the stringency of the hybridization and/or washing 25 conditions, target sequences can be identified which are 100% complementary to the probe (homologous probing). Alternatively, stringency conditions can be adjusted to allow some mismatching in sequences so that lower degrees of similarity are detected (heterologous probing). Generally, a probe is less than about 1000 nucleotides in length, preferably less than 500 nucleotides in length.

30 Typically, stringent conditions will be those in which the salt concentration is less than about 1.5 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (e.g., 10 to 50 nucleotides) and at least about 60°C for long probes (e.g., greater than 50

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- nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. Exemplary low stringency conditions include hybridization with a buffer solution of 30 to 35% formamide, 1 M NaCl, 1% SDS (sodium dodecyl sulphate) at 37°C, and a wash in 1X to 2X SSC (20X SSC = 3.0 M NaCl/0.3 M trisodium citrate) at 50 to 55°C. Exemplary moderate stringency conditions include hybridization in 40 to 45% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.5X to 1X SSC at 55 to 60°C. Exemplary high stringency conditions include hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.1X SSC at 60 to 65°C.
- 10 Specificity is typically the function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. For DNA-DNA hybrids, the T_m can be approximated from the equation of Meinkoth and Wahl, *Anal. Biochem.*, 138:267-284 (1984): $T_m = 81.5^{\circ}\text{C} + 16.6(\log M) + 0.41(\% \text{GC}) - 0.61(\% \text{form}) - 500/L$; where M is the molarity of monovalent cations, %GC is the percentage of guanosine and cytosine nucleotides in the DNA, % form is the percentage of formamide in the hybridization solution, and L is the length of the hybrid in base pairs. The T_m is the temperature (under defined ionic strength and pH) at which 50% of a complementary target sequence hybridizes to a perfectly matched probe. T_m is reduced by about 1 °C for each 1% of mismatching; thus, T_m , hybridization and/or wash conditions can be adjusted to hybridize to sequences of the desired identity. For example, if sequences with $\geq 90\%$ identity are sought, the T_m can be decreased 10 °C. Generally, stringent conditions are selected to be about 5 °C lower than the thermal melting point (T_m) for the specific sequence and its complement at a defined ionic strength and pH. However, severely stringent conditions can utilize a hybridization and/or wash at 1, 2, 3, or 4 °C lower than the thermal melting point (T_m); moderately stringent conditions can utilize a hybridization and/or wash at 6, 7, 8, 9, or 10 °C lower than the thermal melting point (T_m); low stringency conditions can utilize a hybridization and/or wash at 11, 12, 13, 14, 15, or 20 °C lower than the thermal melting point (T_m). Using the equation, hybridization and wash compositions, and desired T_m , those of ordinary skill will understand that variations in the stringency of hybridization and/or wash solutions are inherently described. If the desired degree of mismatching results in a T_m of less than 45 °C (aqueous solution) or 32 °C (formamide solution) it is preferred to increase the SSC concentration so that a higher temperature can be used. An extensive

guide to the hybridization of nucleic acids is found in Tijssen, *Laboratory Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Acid Probes*, Part I, Chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays", Elsevier, New York (1993); and *Current Protocols in Molecular Biology*, 5 Chapter 2, Ausubel, *et al.*, Eds., Greene Publishing and Wiley-Interscience, New York (1995).

As used herein, "transgenic plant" includes reference to a plant which comprises within its genome a heterologous polynucleotide. Generally, the heterologous polynucleotide is stably integrated within the genome such that the polynucleotide is 10 passed on to successive generations. The heterologous polynucleotide may be integrated into the genome alone or as part of a recombinant expression cassette. "Transgenic" is used herein to include any cell, cell line, callus, tissue, plant part or plant, the genotype of which has been altered by the presence of heterologous nucleic acid including those transgenics initially so altered as well as those created by sexual crosses or asexual 15 propagation from the initial transgenic. The term "transgenic" as used herein does not encompass the alteration of the genome (chromosomal or extra-chromosomal) by conventional plant breeding methods or by naturally occurring events such as random cross-fertilization, non-recombinant viral infection, non-recombinant bacterial transformation, non-recombinant transposition, or spontaneous mutation.

20 As used herein, "vector" includes reference to a nucleic acid used in transfection of a host cell and into which can be inserted a polynucleotide. Vectors are often replicons. Expression vectors permit transcription of a nucleic acid inserted therein.

The following terms are used to describe the sequence relationships between two or more nucleic acids or polynucleotides: (a) "reference sequence", (b) "comparison 25 window", (c) "sequence identity", (d) "percentage of sequence identity", and (e) "substantial identity".

(a) As used herein, "reference sequence" is a defined sequence used as a basis for sequence comparison. A reference sequence may be a subset or the entirety of a specified sequence; for example, as a segment of a full-length cDNA or gene sequence, 30 or the complete cDNA or gene sequence.

(b) As used herein, "comparison window" means includes reference to a contiguous and specified segment of a polynucleotide sequence, wherein the polynucleotide sequence may be compared to a reference sequence and wherein the

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portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Generally, the comparison window is at least 20 contiguous nucleotides in length, and optionally 5 can be 30, 40, 50, 100, or longer. Those of skill in the art understand that to avoid a high similarity to a reference sequence due to inclusion of gaps in the polynucleotide sequence a gap penalty is typically introduced and is subtracted from the number of matches.

- Methods of alignment of sequences for comparison are well-known in the art.
- 10 Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman, *Adv. Appl. Math.* 2: 482 (1981); by the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.* 48: 443 (1970); by the search for similarity method of Pearson and Lipman, *Proc. Natl. Acad. Sci.* 85: 2444 (1988); by computerized implementations of these algorithms, including, but not limited
- 15 to: CLUSTAL in the PC/Gene program by Intelligenetics, Mountain View, California, GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, Wisconsin, USA; the CLUSTAL program is well described by Higgins and Sharp, *Gene* 73: 237-244 (1988); Higgins and Sharp, *CABIOS* 5: 151-153 (1989); Corpet, *et al.*, *Nucleic*
- 20 *Acids Research* 16: 10881-90 (1988); Huang, *et al.*, *Computer Applications in the Biosciences* 8: 155-65 (1992), and Pearson, *et al.*, *Methods in Molecular Biology* 24: 307-331 (1994). The BLAST family of programs which can be used for database similarity searches includes: BLASTN for nucleotide query sequences against nucleotide database sequences; BLASTX for nucleotide query sequences against protein database
- 25 sequences; BLASTP for protein query sequences against protein database sequences; TBLASTN for protein query sequences against nucleotide database sequences; and TBLASTX for nucleotide query sequences against nucleotide database sequences. See, *Current Protocols in Molecular Biology*, Chapter 19, Ausubel, *et al.*, Eds., Greene Publishing and Wiley-Interscience, New York (1995).
- 30 Unless otherwise stated, sequence identity/similarity values provided herein refer to the value obtained using the BLAST 2.0 suite of programs using default parameters. Altschul *et al.*, *Nucleic Acids Res.* 25:3389-3402 (1997). Software for performing BLAST analyses is publicly available, e.g., through the National Center for Biotechnology

Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the 5 neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; 10 always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of 15 either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, a cutoff of 100, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 20 scoring matrix (see Henikoff & Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915).

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin & Altschul, *Proc. Nat'l. Acad. Sci. USA* 90:5873-5787 (1993)). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides 25 an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance.

BLAST searches assume that proteins can be modeled as random sequences. However, many real proteins comprise regions of nonrandom sequences which may be homopolymeric tracts, short-period repeats, or regions enriched in one or more amino acids. Such low-complexity regions may be aligned between unrelated proteins even though other regions of the protein are entirely dissimilar. A number of low-complexity filter programs can be employed to reduce such low-complexity alignments. For example, the SEG (Wooten and Federhen, *Comput. Chem.*, 17:149-163 (1993)) and

XNU (Claverie and States, *Comput. Chem.*, 17:191-201 (1993)) low-complexity filters can be employed alone or in combination.

(c) As used herein, "sequence identity" or "identity" in the context of two nucleic acid or polypeptide sequences includes reference to the residues in the two sequences which are the same when aligned for maximum correspondence over a specified comparison window. When percentage of sequence identity is used in reference to proteins it is recognized that residue positions which are not identical often differ by conservative amino acid substitutions, where amino acid residues are substituted for other amino acid residues with similar chemical properties (e.g. charge or hydrophobicity) and therefore do not change the functional properties of the molecule. Where sequences differ in conservative substitutions, the percent sequence identity may be adjusted upwards to correct for the conservative nature of the substitution. Sequences which differ by such conservative substitutions are said to have "sequence similarity" or "similarity". Means for making this adjustment are well-known to those of skill in the art. Typically this involves scoring a conservative substitution as a partial rather than a full mismatch, thereby increasing the percentage sequence identity. Thus, for example, where an identical amino acid is given a score of 1 and a non-conservative substitution is given a score of zero, a conservative substitution is given a score between zero and 1. The scoring of conservative substitutions is calculated, e.g., according to the algorithm of Meyers and Miller, *Computer Applic. Biol. Sci.*, 4: 11-17 (1988) e.g., as implemented in the program PC/GENE (Intelligenetics, Mountain View, California, USA).

(d) As used herein, "percentage of sequence identity" means the value determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

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(e) (i) The term "substantial identity" of polynucleotide sequences means that a polynucleotide comprises a sequence that has at least 70% sequence identity, preferably at least 80%, more preferably at least 90% and most preferably at least 95%, compared to a reference sequence using one of the alignment programs described using standard parameters. One of skill will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like. Substantial identity of amino acid sequences for these purposes normally means sequence identity of at least 60%, more preferably at least 70%, 80%, 90%, and 10 most preferably at least 95%.

Another indication that nucleotide sequences are substantially identical is if two molecules hybridize to each other under stringent conditions. However, nucleic acids which do not hybridize to each other under stringent conditions are still substantially identical if the polypeptides which they encode are substantially identical. This may 15 occur, e.g., when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. One indication that two nucleic acid sequences are substantially identical is that the polypeptide which the first nucleic acid encodes is immunologically cross reactive with the polypeptide encoded by the second nucleic acid.

(e) (ii) The terms "substantial identity" in the context of a peptide indicates that a 20 peptide comprises a sequence with at least 70% sequence identity to a reference sequence, preferably 80%, more preferably 85%, most preferably at least 90% or 95% sequence identity to the reference sequence over a specified comparison window. Preferably, optimal alignment is conducted using the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.* 48: 443 (1970). An indication that two peptide 25 sequences are substantially identical is that one peptide is immunologically reactive with antibodies raised against the second peptide. Thus, a peptide is substantially identical to a second peptide, for example, where the two peptides differ only by a conservative substitution. Peptides which are "substantially similar" share sequences as noted above except that residue positions which are not identical may differ by conservative amino 30 acid changes.

DETAILED DESCRIPTION OF THE INVENTION

Overview

The present invention provides, *among other things*, compositions and methods for modulating (i.e., increasing or decreasing) the level of polypeptides of the present invention in plants. In particular, the polypeptides of the present invention can
5 be expressed at developmental stages, in tissues, and/or in quantities which are uncharacteristic of non-recombinantly engineered plants. Thus, the present invention provides utility in such exemplary applications as improvement of stalk quality for improved stand or silage. Further, the present invention provides for an increased concentration of cellulose in the pericarp; hardening the kernel and thus improving its
10 handling ability.

The present invention also provides isolated nucleic acid comprising polynucleotides of sufficient length and complementarity to a gene of the present invention to use as probes or amplification primers in the detection, quantitation, or isolation of gene transcripts. For example, isolated nucleic acids of the present invention
15 can be used as probes in detecting deficiencies in the level of mRNA in screenings for desired transgenic plants, for detecting mutations in the gene (e.g., substitutions, deletions, or additions), for monitoring upregulation of expression or changes in enzyme activity in screening assays of compounds, for detection of any number of allelic variants (polymorphisms) of the gene, or for use as molecular markers in plant breeding
20 programs. The isolated nucleic acids of the present invention can also be used for recombinant expression of their encoded polypeptides, or for use as immunogens in the preparation and/or screening of antibodies. The isolated nucleic acids of the present invention can also be employed for use in sense or antisense suppression of one or more genes of the present invention in a host cell, tissue, or plant. Attachment of chemical
25 agents which bind, intercalate, cleave and/or crosslink to the isolated nucleic acids of the present invention can also be used to modulate transcription or translation.

The present invention also provides isolated proteins comprising a polypeptide of the present invention (e.g., preproenzyme, proenzyme, or enzymes). The present invention also provides proteins comprising at least one epitope from a polypeptide of the present invention.
30 The proteins of the present invention can be employed in assays for enzyme agonists or antagonists of enzyme function, or for use as immunogens or antigens to obtain antibodies specifically immunoreactive with a protein of the present invention. Such antibodies can be used in assays for expression levels, for identifying

and/or isolating nucleic acids of the present invention from expression libraries, or for purification of polypeptides of the present invention.

The isolated nucleic acids and proteins of the present invention can be used over a broad range of plant types, particularly monocots such as the species of the Family 5 *Graminiae* including *Sorghum bicolor* and *Zea mays*. The isolated nucleic acid and proteins of the present invention can also be used in species from the genera: *Cucurbita*, *Rosa*, *Vitis*, *Juglans*, *Fragaria*, *Lotus*, *Medicago*, *Onobrychis*, *Trifolium*, *Trigonella*, *Vigna*, *Citrus*, *Linum*, *Geranium*, *Manihot*, *Daucus*, *Arabidopsis*, *Brassica*, *Raphanus*, *Sinapis*, *Atropa*, *Capsicum*, *Datura*, *Hyoscyamus*, *Lycopersicon*, *Nicotiana*, *Solanum*, 10 *Petunia*, *Digitalis*, *Majorana*, *Ciahorium*, *Helianthus*, *Lactuca*, *Bromus*, *Asparagus*, *Antirrhinum*, *Heterocallis*, *Nemesis*, *Pelargonium*, *Panieum*, *Pennisetum*, *Ranunculus*, *Senecio*, *Salpiglossis*, *Cucumis*, *Browaalia*, *Glycine*, *Pisum*, *Phaseolus*, *Lolium*, *Oryza*, *Avena*, *Hordeum*, *Secale*, *Triticum*, *Bambusa*, *Dendrocalamus*, and *Melocanna*.

15 **Nucleic Acids**

The present invention provides, *among other things*, isolated nucleic acids of RNA, DNA, and analogs and/or chimeras thereof, comprising a polynucleotide of the present invention.

A polynucleotide of the present invention is inclusive of:

20 (a) a polynucleotide encoding a polypeptide of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58, and conservatively modified and polymorphic variants thereof, including exemplary polynucleotides of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57;

(b) a polynucleotide which is the product of amplification from a *Zea mays* 25 nucleic acid library using primer pairs which selectively hybridize under stringent conditions to loci within a polynucleotide selected from the group consisting of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57, wherein the polynucleotide has substantial sequence identity to a polynucleotide selected from the group consisting of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 30 and 57;

(c) a polynucleotide which selectively hybridizes to a polynucleotide of (a) or (b);

(d) a polynucleotide having a specified sequence identity with polynucleotides of (a), (b), or (c);

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- (e) a polynucleotide encoding a protein having a specified number of contiguous amino acids from a prototype polypeptide, wherein the protein is specifically recognized by antisera elicited by presentation of the protein and wherein the protein does not detectably immunoreact to antisera which has been fully immunosorbed with the protein;
- 5 (f) complementary sequences of polynucleotides of (a), (b), (c), (d), or (e); and
(g) a polynucleotide comprising at least a specific number of contiguous nucleotides from a polynucleotide of (a), (b), (c), (d), (e), or (f).

A. Polynucleotides Encoding A Polypeptide of the Present Invention or Conservatively Modified or Polymorphic Variants Thereof

As indicated in (a), above, the present invention provides isolated nucleic acids comprising a polynucleotide of the present invention, wherein the polynucleotide encodes a polypeptide of the present invention, or conservatively modified or polymorphic variants thereof. Those of skill in the art will recognize that the degeneracy of the genetic code allows for a plurality of polynucleotides to encode for the identical amino acid sequence. Such "silent variations" can be used, for example, to selectively hybridize and detect allelic variants of polynucleotides of the present invention.

Accordingly, the present invention includes polynucleotides of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57, and silent variations of 20 polynucleotides encoding a polypeptide of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58. The present invention further provides isolated nucleic acids comprising polynucleotides encoding conservatively modified variants of a polypeptide of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58. Additionally, the present invention further provides isolated nucleic acids comprising 25 polynucleotides encoding one or more polymorphic (allelic) variants of polypeptides/polynucleotides. Polymorphic variants are frequently used to follow segregation of chromosomal regions in, for example, marker assisted selection methods for crop improvement.

B. Polynucleotides Amplified from a Zea mays Nucleic Acid Library

- As indicated in (b), above, the present invention provides an isolated nucleic acid comprising a polynucleotide of the present invention, wherein the polynucleotides are amplified from a *Zea mays* nucleic acid library. *Zea mays* lines B73, PHRE1, A632, BMS-P2#10, W23, and Mo17 are known and publicly available. Other publicly known and available maize lines can be obtained from the Maize Genetics Cooperation (Urbana, IL). The nucleic acid library may be a cDNA library, a genomic library, or a library generally constructed from nuclear transcripts at any stage of intron processing. cDNA libraries can be normalized to increase the representation of relatively rare cDNAs. In optional embodiments, the cDNA library is constructed using a full-length cDNA synthesis method. Examples of such methods include Oligo-Capping (Maruyama, K. and Sugano, S. *Gene* 138: 171-174, 1994), Biotinylated CAP Trapper (Carninci, P., Kvan, C., et al. *Genomics* 37: 327-336, 1996), and CAP Retention Procedure (Edery, E., Chu, L.L., et al. *Molecular and Cellular Biology* 15: 3363-3371, 1995). cDNA synthesis is often catalyzed at 50-55°C to prevent formation of RNA secondary structure. Examples of reverse transcriptases that are relatively stable at these temperatures are SuperScript II Reverse Transcriptase (Life Technologies, Inc.), AMV Reverse Transcriptase (Boehringer Mannheim) and RetroAmp Reverse Transcriptase (Epicentre). Rapidly growing tissues, or rapidly dividing cells are preferably used as mRNA sources such as from the elongating internode of corn plants.
- The polynucleotides of the present invention include those amplified using the following primer pairs:
- SEQ ID NOS: 3 and 4 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 1;
- SEQ ID NOS: 7 and 8 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 5; and
- SEQ ID NOS: 11 and 12 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 9.
- SEQ ID NOS: 15 and 16 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 13.
- SEQ ID NOS: 19 and 20 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 17;

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SEQ ID NOS: 23 and 24 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 21; and

SEQ ID NOS: 27 and 28 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 25.

5 SEQ ID NOS: 31 and 32 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 29.

SEQ ID NOS: 35 and 36 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 33;

10 SEQ ID NOS: 39 and 40 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 37; and

SEQ ID NOS: 43 and 44 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 41.

SEQ ID NOS: 47 and 48 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 45.

15 SEQ ID NOS: 51 and 52 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 49;

SEQ ID NOS: 55 and 56 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 53; and

20 SEQ ID NOS: 59 and 60 which yield an amplicon comprising a sequence having substantial identity to SEQ ID NO: 57.

The present invention also provides subsequences of the polynucleotides of the present invention. A variety of subsequences can be obtained using primers which selectively hybridize under stringent conditions to at least two sites within a polynucleotide of the present invention, or to two sites within the nucleic acid which 25 flank and comprise a polynucleotide of the present invention, or to a site within a polynucleotide of the present invention and a site within the nucleic acid which comprises it. Primers are chosen to selectively hybridize, under stringent hybridization conditions, to a polynucleotide of the present invention. Generally, the primers are complementary to a subsequence of the target nucleic acid which they amplify. As those skilled in the art will appreciate, the sites to which the primer pairs will selectively 30 hybridize are chosen such that a single contiguous nucleic acid can be formed under the desired amplification conditions.

- In optional embodiments, the primers will be constructed so that they selectively hybridize under stringent conditions to a sequence (or its complement) within the target nucleic acid which comprises the codon encoding the carboxy or amino terminal amino acid residue (i.e., the 3' terminal coding region and 5' terminal coding region, 5 respectively) of the polynucleotides of the present invention. Optionally within these embodiments, the primers will be constructed to selectively hybridize entirely within the coding region of the target polynucleotide of the present invention such that the product of amplification of a cDNA target will consist of the coding region of that cDNA. The primer length in nucleotides is selected from the group of integers consisting of from at 10 least 15 to 50. Thus, the primers can be at least 15, 18, 20, 25, 30, 40, or 50 nucleotides in length. Those of skill will recognize that a lengthened primer sequence can be employed to increase specificity of binding (i.e., annealing) to a target sequence. A non-annealing sequence at the 5'end of a primer (a "tail") can be added, for example, to introduce a cloning site at the terminal ends of the amplicon.
- 15 The amplification products can be translated using expression systems well known to those of skill in the art and as discussed, *infra*. The resulting translation products can be confirmed as polypeptides of the present invention by, for example, assaying for the appropriate catalytic activity (e.g., specific activity and/or substrate specificity), or verifying the presence of one or more linear epitopes which are specific 20 to a polypeptide of the present invention. Methods for protein synthesis from PCR derived templates are known in the art and available commercially. See, e.g., Amersham Life Sciences, Inc, Catalog '97, p.354.

Methods for obtaining 5' and/or 3' ends of a vector insert are well known in the art. See, e.g., RACE (Rapid Amplification of Complementary Ends) as described in 25 Frohman, M. A., in PCR Protocols: A Guide to Methods and Applications, M. A. Innis, D. H. Gelfand, J. J. Sninsky, T. J. White, Eds. (Academic Press, Inc., San Diego, 1990), pp. 28-38.); see also, U.S. Pat. No. 5,470,722, and *Current Protocols in Molecular Biology*, Unit 15.6, Ausubel, *et al.*, Eds., Greene Publishing and Wiley-Interscience, New York (1995); Frohman and Martin, *Techniques* 1:165 (1989).

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C. Polynucleotides Which Selectively Hybridize to a Polynucleotide of (A) or (B)

As indicated in (c), above, the present invention provides isolated nucleic acids comprising polynucleotides of the present invention, wherein the polynucleotides

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selectively hybridize, under selective hybridization conditions, to a polynucleotide of paragraphs (A) or (B) as discussed, *above*. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising the polynucleotides of (A) or (B). For example, polynucleotides of the 5 present invention can be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated or otherwise complementary to a cDNA from a dicot or monocot nucleic acid library. Exemplary species of monocots and dicots include, but are not limited to: corn, canola, soybean, cotton, wheat, sorghum, sunflower, oats, sugar cane, 10 millet, barley, and rice. Optionally, the cDNA library comprises at least 80% full-length sequences, preferably at least 85% or 90% full-length sequences, and more preferably at least 95% full-length sequences. The cDNA libraries can be normalized to increase the representation of rare sequences. Low stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative 15 to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and can be employed to identify orthologous or paralogous sequences.

20 *D. Polynucleotides Having a Specific Sequence Identity with the Polynucleotides of (A), (B) or (C)*

As indicated in (d), *above*, the present invention provides isolated nucleic acids comprising polynucleotides of the present invention, wherein the polynucleotides have a specified identity at the nucleotide level to a polynucleotide as disclosed above in 25 paragraphs (A), (B), or (C). The percentage of identity to a reference sequence is at least 60% and, rounded upwards to the nearest integer, can be expressed as an integer selected from the group of integers consisting of from 60 to 99. Thus, for example, the percentage of identity to a reference sequence can be at least 70%, 75%, 80%, 85%, 90%, or 95%.

30 Optionally, the polynucleotides of this embodiment will share an epitope with a polypeptide encoded by the polynucleotides of (A), (B), or (C). Thus, these polynucleotides encode a first polypeptide which elicits production of antisera comprising antibodies which are specifically reactive to a second polypeptide encoded by

- a polynucleotide of (A), (B), or (C). However, the first polypeptide does not bind to antisera raised against itself when the antisera has been fully immunosorbed with the first polypeptide. Hence, the polynucleotides of this embodiment can be used to generate antibodies for use in, for example, the screening of expression libraries for nucleic acids
- 5 comprising polynucleotides of (A), (B), or (C), or for purification of, or in immunoassays for, polypeptides encoded by the polynucleotides of (A), (B), or (C). The polynucleotides of this embodiment embrace nucleic acid sequences which can be employed for selective hybridization to a polynucleotide encoding a polypeptide of the present invention.
- 10 Screening polypeptides for specific binding to antisera can be conveniently achieved using peptide display libraries. This method involves the screening of large collections of peptides for individual members having the desired function or structure. Antibody screening of peptide display libraries is well known in the art. The displayed peptide sequences can be from 3 to 5000 or more amino acids in length, frequently from
- 15 5-100 amino acids long, and often from about 8 to 15 amino acids long. In addition to direct chemical synthetic methods for generating peptide libraries, several recombinant DNA methods have been described. One type involves the display of a peptide sequence on the surface of a bacteriophage or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular displayed peptide sequence. Such
- 20 methods are described in PCT patent publication Nos. 91/17271, 91/18980, 91/19818, and 93/08278. Other systems for generating libraries of peptides have aspects of both *in vitro* chemical synthesis and recombinant methods. See, PCT Patent publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754; and 5,643,768. Peptide display libraries, vectors, and screening kits are commercially
- 25 available from such suppliers as Invitrogen (Carlsbad, CA).

E. Polynucleotides Encoding a Protein Having a Subsequence from a Prototype Polypeptide and is Cross-Reactive to the Prototype Polypeptide

- As indicated in (e), above, the present invention provides isolated nucleic acids
- 30 comprising polynucleotides of the present invention, wherein the polynucleotides encode a protein having a subsequence of contiguous amino acids from a prototype polypeptide of the present invention such as are provided in (a), above. The length of contiguous amino acids from the prototype polypeptide is selected from the group of integers

consisting of from at least 10 to the number of amino acids within the prototype sequence. Thus, for example, the polynucleotide can encode a polypeptide having a subsequence having at least 10, 15, 20, 25, 30, 35, 40, 45, or 50, contiguous amino acids from the prototype polypeptide. Further, the number of such subsequences 5 encoded by a polynucleotide of the instant embodiment can be any integer selected from the group consisting of from 1 to 20, such as 2, 3, 4, or 5. The subsequences can be separated by any integer of nucleotides from 1 to the number of nucleotides in the sequence such as at least 5, 10, 15, 25, 50, 100, or 200 nucleotides.

The proteins encoded by polynucleotides of this embodiment, when presented as 10 an immunogen, elicit the production of polyclonal antibodies which specifically bind to a prototype polypeptide such as but not limited to, a polypeptide encoded by the polynucleotide of (a) or (b), above. Generally, however, a protein encoded by a polynucleotide of this embodiment does not bind to antisera raised against the prototype polypeptide when the antisera has been fully immunosorbed with the prototype 15 polypeptide. Methods of making and assaying for antibody binding specificity/affinity are well known in the art. Exemplary immunoassay formats include ELISA, competitive immunoassays, radioimmunoassays, Western blots, indirect immunofluorescent assays and the like.

In a preferred assay method, fully immunosorbed and pooled antisera which is 20 elicited to the prototype polypeptide can be used in a competitive binding assay to test the protein. The concentration of the prototype polypeptide required to inhibit 50% of the binding of the antisera to the prototype polypeptide is determined. If the amount of the protein required to inhibit binding is less than twice the amount of the prototype protein, then the protein is said to specifically bind to the antisera elicited to the 25 immunogen. Accordingly, the proteins of the present invention embrace allelic variants, conservatively modified variants, and minor recombinant modifications to a prototype polypeptide.

A polynucleotide of the present invention optionally encodes a protein having a molecular weight as the non-glycosylated protein within 20% of the molecular weight of 30 the full-length non-glycosylated polypeptides of the present invention. Molecular weight can be readily determined by SDS-PAGE under reducing conditions. Preferably, the molecular weight is within 15% of a full length polypeptide of the present invention, more preferably within 10% or 5%, and most preferably within 3%, 2%, or 1% of a full

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length polypeptide of the present invention. Molecular weight determination of a protein can be conveniently performed by SDS-PAGE under denaturing conditions.

- Optionally, the polynucleotides of this embodiment will encode a protein having a specific activity at least 50%, 60%, 80%, or 90% of the native, endogenous (i.e., non-isolated), full-length polypeptide of the present invention. Further, the proteins encoded by polynucleotides of this embodiment will optionally have a substantially similar affinity constant (K_m) and/or catalytic activity (i.e., the microscopic rate constant, k_{cat}) as the native endogenous, full-length protein. Those of skill in the art will recognize that k_{cat}/K_m value determines the specificity for competing substrates and is often referred to as the specificity constant. Proteins of this embodiment can have a k_{cat}/K_m value at least 10% of a non-isolated full-length polypeptide of the present invention as determined using the endogenous substrate of that polypeptide. Optionally, the k_{cat}/K_m value will be at least 20%, 30%, 40%, 50%, and most preferably at least 60%, 70%, 80%, 90%, or 95% the k_{cat}/K_m value of the non-isolated, full-length polypeptide of the present invention.
- Determination of k_{cat} , K_m , and k_{cat}/K_m can be determined by any number of means well known to those of skill in the art. For example, the initial rates (i.e., the first 5% or less of the reaction) can be determined using rapid mixing and sampling techniques (e.g., continuous-flow, stopped-flow, or rapid quenching techniques), flash photolysis, or relaxation methods (e.g., temperature jumps) in conjunction with such exemplary methods of measuring as spectrophotometry, spectrofluorimetry, nuclear magnetic resonance, or radioactive procedures. Kinetic values are conveniently obtained using a Lineweaver-Burk or Eadie-Hofstee plot.

F. Polynucleotides Complementary to the Polynucleotides of (A)-(E)

- As indicated in (f), above, the present invention provides isolated nucleic acids comprising polynucleotides complementary to the polynucleotides of paragraphs A-E, above. As those of skill in the art will recognize, complementary sequences base-pair throughout the entirety of their length with the polynucleotides of (A)-(E) (i.e., have 100% sequence identity over their entire length). Complementary bases associate through hydrogen bonding in double stranded nucleic acids. For example, the following base pairs are complementary: guanine and cytosine; adenine and thymine; and adenine and uracil.

G. Polynucleotides Which are Subsequences of the Polynucleotides of (A)-(F)

As indicated in (g), above, the present invention provides isolated nucleic acids comprising polynucleotides which comprise at least 15 contiguous bases from the polynucleotides of (A) through (F) as discussed above. The length of the polynucleotide
5 is given as an integer selected from the group consisting of from at least 15 to the length of the nucleic acid sequence from which the polynucleotide is a subsequence of. Thus, for example, polynucleotides of the present invention are inclusive of polynucleotides comprising at least 15, 20, 25, 30, 40, 50, 60, 75, or 100 contiguous nucleotides in length from the polynucleotides of (A)-(F). Optionally, the number of such
10 subsequences encoded by a polynucleotide of the instant embodiment can be any integer selected from the group consisting of from 1 to 20, such as 2, 3, 4, or 5. The subsequences can be separated by any integer of nucleotides from 1 to the number of nucleotides in the sequence such as at least 5, 10, 15, 25, 50, 100, or 200 nucleotides.

The subsequences of the present invention can comprise structural characteristics
15 of the sequence from which it is derived. Alternatively, the subsequences can lack certain structural characteristics of the larger sequence from which it is derived. For example, a subsequence from a polynucleotide encoding a polypeptide having at least one linear epitope in common with a prototype polypeptide sequence as provided in (a), above, may encode an epitope in common with the prototype sequence. Alternatively,
20 the subsequence may not encode an epitope in common with the prototype sequence but can be used to isolate the larger sequence by, for example, nucleic acid hybridization with the sequence from which it's derived. Subsequences can be used to modulate or detect gene expression by introducing into the subsequences compounds which bind, intercalate, cleave and/or crosslink to nucleic acids. Exemplary compounds include
25 acridine, psoralen, phenanthroline, naphthoquinone, daunomycin or chloroethylaminoaryl conjugates.

Construction of Nucleic Acids

The isolated nucleic acids of the present invention can be made using (a) standard
30 recombinant methods, (b) synthetic techniques, or combinations thereof. In some embodiments, the polynucleotides of the present invention will be cloned, amplified, or otherwise constructed from a monocot. In preferred embodiments the monocot is *Zea mays*.

The nucleic acids may conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites may be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences may be inserted to aid in 5 the isolation of the translated polynucleotide of the present invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the proteins of the present invention. A polynucleotide of the present invention can be attached to a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention. Additional sequences may be added to such cloning and/or expression 10 sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Typically, the length of a nucleic acid of the present invention less the length of its polynucleotide of the present invention is less than 20 kilobase pairs, often less than 15 kb, and frequently less than 10 kb. Use of cloning vectors, expression vectors, adapters, 15 and linkers is well known and extensively described in the art. For a description of various nucleic acids see, for example, Stratagene Cloning Systems, Catalogs 1995, 1996, 1997 (La Jolla, CA); and, Amersham Life Sciences, Inc, Catalog '97 (Arlington Heights, IL).

20 *A. Recombinant Methods for Constructing Nucleic Acids*

The isolated nucleic acid compositions of this invention, such as RNA, cDNA, genomic DNA, or a hybrid thereof, can be obtained from plant biological sources using any number of cloning methodologies known to those of skill in the art. In some embodiments, oligonucleotide probes which selectively hybridize, under stringent 25 conditions, to the polynucleotides of the present invention are used to identify the desired sequence in a cDNA or genomic DNA library. While isolation of RNA, and construction of cDNA and genomic libraries is well known to those of ordinary skill in the art, the following highlights some of the methods employed.

30 *A1. mRNA Isolation and Purification*

Total RNA from plant cells comprises such nucleic acids as mitochondrial RNA, chloroplastic RNA, rRNA, tRNA, hnRNA and mRNA. Total RNA preparation typically involves lysis of cells and removal of proteins, followed by precipitation of nucleic

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acids. Extraction of total RNA from plant cells can be accomplished by a variety of means. Frequently, extraction buffers include a strong detergent such as SDS and an organic denaturant such as guanidinium isothiocyanate, guanidine hydrochloride or phenol. Following total RNA isolation, poly(A)⁺ mRNA is typically purified from the remainder RNA using oligo(dT) cellulose. Exemplary total RNA and mRNA isolation protocols are described in *Plant Molecular Biology: A Laboratory Manual*, Clark, Ed., Springer-Verlag, Berlin (1997); and, *Current Protocols in Molecular Biology*, Ausubel, et al., Eds., Greene Publishing and Wiley-Interscience, New York (1995). Total RNA and mRNA isolation kits are commercially available from vendors such as Stratagene (La Jolla, CA), Clonetech (Palo Alto, CA), Pharmacia (Piscataway, NJ), and 5'-3' (Paoli, PA). See also, U.S. Patent Nos. 5,614,391; and, 5,459,253. The mRNA can be fractionated into populations with size ranges of about 0.5, 1.0, 1.5, 2.0, 2.5 or 3.0 kb. The cDNA synthesized for each of these fractions can be size selected to the same size range as its mRNA prior to vector insertion. This method helps eliminate truncated cDNA formed by incompletely reverse transcribed mRNA.

A2. Construction of a cDNA Library

Construction of a cDNA library generally entails five steps. First, first strand cDNA synthesis is initiated from a poly(A)⁺ mRNA template using a poly(dT) primer or random hexanucleotides. Second, the resultant RNA-DNA hybrid is converted into double stranded cDNA, typically by a combination of RNase H and DNA polymerase I (or Klenow fragment). Third, the termini of the double stranded cDNA are ligated to adaptors. Ligation of the adaptors will produce cohesive ends for cloning. Fourth, size selection of the double stranded cDNA eliminates excess adaptors and primer fragments, and eliminates partial cDNA molecules due to degradation of mRNAs or the failure of reverse transcriptase to synthesize complete first strands. Fifth, the cDNAs are ligated into cloning vectors and packaged. cDNA synthesis protocols are well known to the skilled artisan and are described in such standard references as: *Plant Molecular Biology: A Laboratory Manual*, Clark, Ed., Springer-Verlag, Berlin (1997); and, *Current Protocols in Molecular Biology*, Ausubel, et al., Eds., Greene Publishing and Wiley-Interscience, New York (1995). cDNA synthesis kits are available from a variety of commercial vendors such as Stratagene or Pharmacia.

A number of cDNA synthesis protocols have been described which provide substantially pure full-length cDNA libraries. Substantially pure full-length cDNA libraries are constructed to comprise at least 90%, and more preferably at least 93% or 95% full-length inserts amongst clones containing inserts. The length of insert in such 5 libraries can be from 0 to 8, 9, 10, 11, 12, 13, or more kilobase pairs. Vectors to accommodate inserts of these sizes are known in the art and available commercially. See, e.g., Stratagene's lambda ZAP Express (cDNA cloning vector with 0 to 12 kb cloning capacity).

An exemplary method of constructing a greater than 95% pure full-length cDNA 10 library is described by Carninci *et al.*, *Genomics*, 37:327-336 (1996). In that protocol, the cap-structure of eukaryotic mRNA is chemically labeled with biotin. By using streptavidin-coated magnetic beads, only the full-length first-strand cDNA/mRNA hybrids are selectively recovered after RNase I treatment. The method provides a high yield library with an unbiased representation of the starting mRNA population. Other 15 methods for producing full-length libraries are known in the art. See, e.g., Edery *et al.*, *Mol. Cell Biol.*, 15(6):3363-3371 (1995); and, PCT Application WO 96/34981.

A3. Normalized or Subtracted cDNA Libraries

A non-normalized cDNA library represents the mRNA population of the tissue it 20 was made from. Since unique clones are out-numbered by clones derived from highly expressed genes their isolation can be laborious. Normalization of a cDNA library is the process of creating a library in which each clone is more equally represented.

A number of approaches to normalize cDNA libraries are known in the art. One approach is based on hybridization to genomic DNA. The frequency of each hybridized 25 cDNA in the resulting normalized library would be proportional to that of each corresponding gene in the genomic DNA. Another approach is based on kinetics. If cDNA reannealing follows second-order kinetics, rarer species anneal less rapidly and the remaining single-stranded fraction of cDNA becomes progressively more normalized during the course of the hybridization. Specific loss of any species of cDNA, regardless 30 of its abundance, does not occur at any Cot value. Construction of normalized libraries is described in Ko, *Nucl. Acids. Res.*, 18(19):5705-5711 (1990); Patanjali *et al.*, *Proc. Natl. Acad. U.S.A.*, 88:1943-1947 (1991); U.S. Patents 5,482,685, and 5,637,685. In an exemplary method described by Soares *et al.*, normalization resulted in reduction of

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the abundance of clones from a range of four orders of magnitude to a narrow range of only 1 order of magnitude. *Proc. Natl. Acad. Sci. USA*, 91:9228-9232 (1994).

Subtracted cDNA libraries are another means to increase the proportion of less abundant cDNA species. In this procedure, cDNA prepared from one pool of mRNA is 5 depleted of sequences present in a second pool of mRNA by hybridization. The cDNA:mRNA hybrids are removed and the remaining un-hybridized cDNA pool is enriched for sequences unique to that pool. See, *Foote et al.* in, *Plant Molecular Biology: A Laboratory Manual*, Clark, Ed., Springer-Verlag, Berlin (1997); Kho and Zarbl, *Technique*, 3(2):58-63 (1991); Sive and St. John, *Nucl. Acids Res.*, 16(22):10937 10 (1988); *Current Protocols in Molecular Biology*, Ausubel, *et al.*, Eds., Greene Publishing and Wiley-Interscience, New York (1995); and, Swaroop *et al.*, *Nucl. Acids Res.*, 19(8):1954 (1991). cDNA subtraction kits are commercially available. See, e.g., PCR-Select (Clontech).

15 *A4. Construction of a Genomic Library*

To construct genomic libraries, large segments of genomic DNA are generated by random fragmentation, e.g. using restriction endonucleases, and are ligated with vector DNA to form concatemers that can be packaged into the appropriate vector. Methodologies to accomplish these ends, and sequencing methods to verify the sequence 20 of nucleic acids are well known in the art. Examples of appropriate molecular biological techniques and instructions sufficient to direct persons of skill through many construction, cloning, and screening methodologies are found in Sambrook, *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory Vols. 1-3 (1989), *Methods in Enzymology*, Vol. 152: *Guide to Molecular Cloning Techniques*, Berger and Kimmel, Eds., San Diego: Academic Press, Inc. (1987), *Current Protocols in Molecular Biology*, Ausubel, *et al.*, Eds., Greene Publishing and Wiley-Interscience, New York (1995); *Plant Molecular Biology: A Laboratory Manual*, Clark, Ed., Springer-Verlag, Berlin (1997). Kits for construction of genomic libraries are also 25 commercially available.

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A5. Nucleic Acid Screening and Isolation Methods

The cDNA or genomic library can be screened using a probe based upon the sequence of a polynucleotide of the present invention such as those disclosed herein.

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Probes may be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different plant species. Those of skill in the art will appreciate that various degrees of stringency of hybridization can be employed in the assay; and either the hybridization or the wash medium can be stringent. As the 5 conditions for hybridization become more stringent, there must be a greater degree of complementarity between the probe and the target for duplex formation to occur. The degree of stringency can be controlled by temperature, ionic strength, pH and the presence of a partially denaturing solvent such as formamide. For example, the stringency of hybridization is conveniently varied by changing the polarity of the reactant 10 solution through manipulation of the concentration of formamide within the range of 0% to 50%. The degree of complementarity (sequence identity) required for detectable binding will vary in accordance with the stringency of the hybridization medium and/or wash medium. The degree of complementarity will optimally be 100 percent; however, it should be understood that minor sequence variations in the probes and primers may be 15 compensated for by reducing the stringency of the hybridization and/or wash medium.

The nucleic acids of interest can also be amplified from nucleic acid samples using amplification techniques. For instance, polymerase chain reaction (PCR) technology can be used to amplify the sequences of polynucleotides of the present invention and related genes directly from genomic DNA or cDNA libraries. PCR and 20 other *in vitro* amplification methods may also be useful, for example, to clone nucleic acid sequences that code for proteins to be expressed, to make nucleic acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes. Examples of techniques sufficient to direct persons of skill through *in vitro* amplification methods are found in Berger, Sambrook, and 25 Ausubel, as well as Mullis *et al.*, U.S. Patent No. 4,683,202 (1987); and, *PCR Protocols A Guide to Methods and Applications*, Innis *et al.*, Eds., Academic Press Inc., San Diego, CA (1990). Commercially available kits for genomic PCR amplification are known in the art. See, e.g., Advantage-GC Genomic PCR Kit (Clontech). The T4 gene 32 protein (Boehringer Mannheim) can be used to improve yield of long PCR products.

30 PCR-based screening methods have also been described. Wilfinger *et al.* describe a PCR-based method in which the longest cDNA is identified in the first step so that incomplete clones can be eliminated from study. *BioTechniques*, 22(3): 481-486 (1997). In that method, a primer pair is synthesized with one primer annealing to the 5'

end of the sense strand of the desired cDNA and the other primer to the vector. Clones are pooled to allow large-scale screening. By this procedure, the longest possible clone is identified amongst candidate clones. Further, the PCR product is used solely as a diagnostic for the presence of the desired cDNA and does not utilize the PCR product 5 itself. Such methods are particularly effective in combination with a full-length cDNA construction methodology, above.

B. Synthetic Methods for Constructing Nucleic Acids

The isolated nucleic acids of the present invention can also be prepared by direct 10 chemical synthesis by methods such as the phosphotriester method of Narang *et al.*, *Meth. Enzymol.* 68: 90-99 (1979); the phosphodiester method of Brown *et al.*, *Meth. Enzymol.* 68: 109-151 (1979); the diethylphosphoramidite method of Beaucage *et al.*, *Tetra. Lett.* 22: 1859-1862 (1981); the solid phase phosphoramidite triester method described by Beaucage and Caruthers, *Tetra. Letts.* 22(20): 1859-1862 (1981), e.g., 15 using an automated synthesizer, e.g., as described in Needham-VanDevanter *et al.*, *Nucleic Acids Res.*, 12: 6159-6168 (1984); and, the solid support method of U.S. Patent No. 4,458,066. Chemical synthesis generally produces a single stranded oligonucleotide. This may be converted into double stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the 20 single strand as a template. One of skill will recognize that while chemical synthesis of DNA is limited to sequences of about 100 bases, longer sequences may be obtained by the ligation of shorter sequences.

Recombinant Expression Cassettes

25 The present invention further provides recombinant expression cassettes comprising a nucleic acid of the present invention. A nucleic acid sequence coding for the desired polynucleotide of the present invention, for example a cDNA or a genomic sequence encoding a full length polypeptide of the present invention, can be used to construct a recombinant expression cassette which can be introduced into the desired host 30 cell. A recombinant expression cassette will typically comprise a polynucleotide of the present invention operably linked to transcriptional initiation regulatory sequences which will direct the transcription of the polynucleotide in the intended host cell, such as tissues of a transformed plant.

For example, plant expression vectors may include (1) a cloned plant gene under the transcriptional control of 5' and 3' regulatory sequences and (2) a dominant selectable marker. Such plant expression vectors may also contain, if desired, a promoter regulatory region (e.g., one conferring inducible or constitutive, environmentally- or 5 developmentally-regulated, or cell- or tissue-specific/selective expression), a transcription initiation start site, a ribosome binding site, an RNA processing signal, a transcription termination site, and/or a polyadenylation signal.

A plant promoter fragment can be employed which will direct expression of a polynucleotide of the present invention in all tissues of a regenerated plant. Such 10 promoters are referred to herein as "constitutive" promoters and are active under most environmental conditions and states of development or cell differentiation. Examples of constitutive promoters include the cauliflower mosaic virus (CaMV) 35S transcription initiation region, the 1'- or 2'- promoter derived from T-DNA of *Agrobacterium tumefaciens*, the ubiquitin 1 promoter, the Smas promoter, the cinnamyl alcohol 15 dehydrogenase promoter (U.S. Patent No. 5,683,439), the *Nos* promoter, the pEmu promoter, the rubisco promoter, the GRP1-8 promoter, the actin promoter, the F3.7 promoter, and other transcription initiation regions from various plant genes known to those of skill.

Alternatively, the plant promoter can direct expression of a polynucleotide of the 20 present invention in a specific tissue or may be otherwise under more precise environmental or developmental control. Such promoters are referred to here as "inducible" promoters. Environmental conditions that may effect transcription by inducible promoters include pathogen attack, anaerobic conditions, or the presence of light. Examples of inducible promoters are the *Adh1* promoter which is inducible by 25 hypoxia or cold stress, the *Hsp70* promoter which is inducible by heat stress, and the *PPDK* promoter which is inducible by light.

Examples of promoters under developmental control include promoters that 30 initiate transcription only, or preferentially, in certain tissues, such as leaves, roots, fruit, seeds, or flowers. The operation of a promoter may also vary depending on its location in the genome. Thus, an inducible promoter may become fully or partially constitutive in certain locations.

Both heterologous and non-heterologous (i.e., endogenous) promoters can be employed to direct expression of the nucleic acids of the present invention. These

promoters can also be used, for example, in recombinant expression cassettes to drive expression of antisense nucleic acids to reduce, increase, or alter concentration and/or composition of the proteins of the present invention in a desired tissue. Thus, in some embodiments, the nucleic acid construct will comprise a promoter functional in a plant cell, such as in *Zea mays*, operably linked to a polynucleotide of the present invention. Promoters useful in these embodiments include the endogenous promoters driving expression of a polypeptide of the present invention.

In some embodiments, isolated nucleic acids which serve as promoter or enhancer elements can be introduced in the appropriate position (generally upstream) of a non-heterologous form of a polynucleotide of the present invention so as to up or down regulate expression of a polynucleotide of the present invention. For example, endogenous promoters can be altered *in vivo* by mutation, deletion, and/or substitution (see, Kmiec, U.S. Patent 5,565,350; Zarling *et al.*, PCT/US93/03868), or isolated promoters can be introduced into a plant cell in the proper orientation and distance from a gene of the present invention so as to control the expression of the gene. Gene expression can be modulated under conditions suitable for plant growth so as to alter the total concentration and/or alter the composition of the polypeptides of the present invention in plant cell. Thus, the present invention provides compositions, and methods for making, heterologous promoters and/or enhancers operably linked to a native, endogenous (i.e., non-heterologous) form of a polynucleotide of the present invention.

Methods for identifying promoters with a particular expression pattern, in terms of, e.g., tissue type, cell type, stage of development, and/or environmental conditions, are well known in the art. See, e.g., *The Maize Handbook*, Chapters 114-115, Freeling and Walbot, Eds., Springer, New York (1994); *Corn and Corn Improvement*, 3rd edition, Chapter 6, Sprague and Dudley, Eds., American Society of Agronomy, Madison, Wisconsin (1988). A typical step in promoter isolation methods is identification of gene products that are expressed with some degree of specificity in the target tissue. Amongst the range of methodologies are: differential hybridization to cDNA libraries; subtractive hybridization; differential display; differential 2-D protein gel electrophoresis; DNA probe arrays; and isolation of proteins known to be expressed with some specificity in the target tissue. Such methods are well known to those of skill in the art. Commercially available products for identifying promoters are known in the art such as Clontech's (Palo Alto, CA) Universal GenomeWalker Kit.

For the protein-based methods, it is helpful to obtain the amino acid sequence for at least a portion of the identified protein, and then to use the protein sequence as the basis for preparing a nucleic acid that can be used as a probe to identify either genomic DNA directly, or preferably, to identify a cDNA clone from a library prepared from the target tissue. Once such a cDNA clone has been identified, that sequence can be used to identify the sequence at the 5' end of the transcript of the indicated gene. For differential hybridization, subtractive hybridization and differential display, the nucleic acid sequence identified as enriched in the target tissue is used to identify the sequence at the 5' end of the transcript of the indicated gene. Once such sequences are identified, starting either from protein sequences or nucleic acid sequences, any of these sequences identified as being from the gene transcript can be used to screen a genomic library prepared from the target organism. Methods for identifying and confirming the transcriptional start site are well known in the art.

In the process of isolating promoters expressed under particular environmental conditions or stresses, or in specific tissues, or at particular developmental stages, a number of genes are identified that are expressed under the desired circumstances, in the desired tissue, or at the desired stage. Further analysis will reveal expression of each particular gene in one or more other tissues of the plant. One can identify a promoter with activity in the desired tissue or condition but that do not have activity in any other common tissue.

To identify the promoter sequence, the 5' portions of the clones described here are analyzed for sequences characteristic of promoter sequences. For instance, promoter sequence elements include the TATA box consensus sequence (TATAAT), which is usually an AT-rich stretch of 5-10 bp located approximately 20 to 40 base pairs upstream of the transcription start site. Identification of the TATA box is well known in the art. For example, one way to predict the location of this element is to identify the transcription start site using standard RNA-mapping techniques such as primer extension, S1 analysis, and/or RNase protection. To confirm the presence of the AT-rich sequence, a structure-function analysis can be performed involving mutagenesis of the putative region and quantification of the mutation's effect on expression of a linked downstream reporter gene. See, e.g., *The Maize Handbook*, Chapter 114, Freeling and Walbot, Eds., Springer, New York, (1994).

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In plants, further upstream from the TATA box, at positions -80 to -100, there is typically a promoter element (i.e., the CAAT box) with a series of adenines surrounding the trinucleotide G (or T) N G. J. Messing *et al.*, in *Genetic Engineering in Plants*, Kosage, Meredith and Hollaender, Eds., pp. 221-227 1983. In maize, there is no well 5 conserved CAAT box but there are several short, conserved protein-binding motifs upstream of the TATA box. These include motifs for the trans-acting transcription factors involved in light regulation, anaerobic induction, hormonal regulation, or anthocyanin biosynthesis, as appropriate for each gene.

Once promoter and/or gene sequences are known, a region of suitable size 10 is selected from the genomic DNA that is 5' to the transcriptional start, or the translational start site, and such sequences are then linked to a coding sequence. If the transcriptional start site is used as the point of fusion, any of a number of possible 5' untranslated regions can be used in between the transcriptional start site and the partial coding sequence. If the translational start site at the 3' end of the specific promoter is 15 used, then it is linked directly to the methionine start codon of a coding sequence.

If polypeptide expression is desired, it is generally desirable to include a polyadenylation region at the 3'-end of a polynucleotide coding region. The polyadenylation region can be derived from the natural gene, from a variety of other plant genes, or from T-DNA. The 3' end sequence to be added can be derived from, for 20 example, the nopaline synthase or octopine synthase genes, or alternatively from another plant gene, or less preferably from any other eukaryotic gene.

An intron sequence can be added to the 5' untranslated region or the coding sequence of the partial coding sequence to increase the amount of the mature message that accumulates in the cytosol. Inclusion of a spliceable intron in the 25 transcription unit in both plant and animal expression constructs has been shown to increase gene expression at both the mRNA and protein levels up to 1000-fold. Buchman and Berg, *Mol. Cell Biol.* 8: 4395-4405 (1988); Callis *et al.*, *Genes Dev.* 1: 1183-1200 (1987). Such intron enhancement of gene expression is typically greatest when placed near the 5' end of the transcription unit. Use of maize introns Adh1-S intron 1, 2, and 30 6, the Bronze-1 intron are known in the art. See generally, *The Maize Handbook*, Chapter 116, Freeling and Walbot, Eds., Springer, New York (1994).

The vector comprising the sequences from a polynucleotide of the present invention will typically comprise a marker gene which confers a selectable phenotype on

- plant cells. Usually, the selectable marker gene will encode antibiotic resistance, with suitable genes including genes coding for resistance to the antibiotic spectinomycin (e.g., the *aada* gene), the streptomycin phosphotransferase (SPT) gene coding for streptomycin resistance, the neomycin phosphotransferase (NPTII) gene encoding kanamycin or 5 geneticin resistance, the hygromycin phosphotransferase (HPT) gene coding for hygromycin resistance, genes coding for resistance to herbicides which act to inhibit the action of acetolactate synthase (ALS), in particular the sulfonylurea-type herbicides (e.g., the acetolactate synthase (ALS) gene containing mutations leading to such 10 resistance in particular the S4 and/or Hra mutations), genes coding for resistance to herbicides which act to inhibit action of glutamine synthase, such as phosphinothricin or basta (e.g., the *bar* gene), or other such genes known in the art. The *bar* gene encodes 15 resistance to the herbicide basta, the *nptII* gene encodes resistance to the antibiotics kanamycin and geneticin, and the ALS gene encodes resistance to the herbicide chlorsulfuron.
- 15 Typical vectors useful for expression of genes in higher plants are well known in the art and include vectors derived from the tumor-inducing (Ti) plasmid of *Agrobacterium tumefaciens* described by Rogers *et al.*, Meth. In Enzymol., 153:253-277 (1987). These vectors are plant integrating vectors in that on transformation, the vectors integrate a portion of vector DNA into the genome of the host plant. Exemplary A. 20 *tumefaciens* vectors useful herein are plasmids pKYLX6 and pKYLX7 of Schardl *et al.*, Gene, 61:1-11 (1987) and Berger *et al.*, Proc. Natl. Acad. Sci. U.S.A., 86:8402-8406 (1989). Another useful vector herein is plasmid pBI101.2 that is available from Clontech Laboratories, Inc. (Palo Alto, CA).
- 25 A polynucleotide of the present invention can be expressed in either sense or anti-sense orientation as desired. It will be appreciated that control of gene expression in either sense or anti-sense orientation can have a direct impact on the observable plant characteristics. Antisense technology can be conveniently used to gene expression in plants. To accomplish this, a nucleic acid segment from the desired gene is cloned and operably linked to a promoter such that the anti-sense strand of RNA will be transcribed.
- 30 The construct is then transformed into plants and the antisense strand of RNA is produced. In plant cells, it has been shown that antisense RNA inhibits gene expression by preventing the accumulation of mRNA which encodes the enzyme of interest, see,

e.g., Sheehy *et al.*, *Proc. Nat'l. Acad. Sci. (USA)* 85: 8805-8809 (1988); and Hiatt *et al.*, U.S. Patent No. 4,801,340.

Another method of suppression is sense suppression. Introduction of nucleic acid configured in the sense orientation has been shown to be an effective means by which to 5 block the transcription of target genes. For an example of the use of this method to modulate expression of endogenous genes see, Napoli *et al.*, *The Plant Cell* 2: 279-289 (1990) and U.S. Patent No. 5,034,323.

Catalytic RNA molecules or ribozymes can also be used to inhibit expression of 10 plant genes. It is possible to design ribozymes that specifically pair with virtually any target RNA and cleave the phosphodiester backbone at a specific location, thereby 15 functionally inactivating the target RNA. In carrying out this cleavage, the ribozyme is not itself altered, and is thus capable of recycling and cleaving other molecules, making it a true enzyme. The inclusion of ribozyme sequences within antisense RNAs confers RNA-cleaving activity upon them, thereby increasing the activity of the constructs. The 20 design and use of target RNA-specific ribozymes is described in Haseloff *et al.*, *Nature* 334: 585-591 (1988).

A variety of cross-linking agents, alkylating agents and radical generating species 25 as pendant groups on polynucleotides of the present invention can be used to bind, label, detect, and/or cleave nucleic acids. For example, Vlassov, V. V., *et al.*, *Nucleic Acids Res* (1986) 14:4065-4076, describe covalent bonding of a single-stranded DNA fragment with alkylating derivatives of nucleotides complementary to target sequences. A report of similar work by the same group is that by Knorre, D. G., *et al.*, *Biochimie* (1985) 67:785-789. Iverson and Dervan also showed sequence-specific cleavage of single-stranded DNA mediated by incorporation of a modified nucleotide which was capable of activating cleavage (*J Am Chem Soc* (1987) 109:1241-1243). Meyer, R. B., *et al.*, *J Am Chem Soc* (1989) 111:8517-8519, effect covalent crosslinking to a target nucleotide using an alkylating agent complementary to the single-stranded target nucleotide sequence. A photoactivated crosslinking to single-stranded oligonucleotides mediated by psoralen was disclosed by Lee, B. L., *et al.*, *Biochemistry* (1988) 27:3197-3203. Use of crosslinking 30 in triple-helix forming probes was also disclosed by Home, *et al.*, *J Am Chem Soc* (1990) 112:2435-2437. Use of N4, N4-ethanocytosine as an alkylating agent to crosslink to single-stranded oligonucleotides has also been described by Webb and Matteucci, *J Am Chem Soc* (1986) 108:2764-2765; *Nucleic Acids Res* (1986) 14:7661-7674; Feteritz

et al., *J. Am. Chem. Soc.* 113:4000 (1991). Various compounds to bind, detect, label, and/or cleave nucleic acids are known in the art. See, for example, U.S. Patent Nos. 5,543,507; 5,672,593; 5,484,908; 5,256,648; and, 5,681941.

5 **Proteins**

- The isolated proteins of the present invention comprise a polypeptide having at least 10 amino acids encoded by any one of the polynucleotides of the present invention as discussed more fully, above, or polypeptides which are conservatively modified variants thereof. The proteins of the present invention or variants thereof can comprise
10 any number of contiguous amino acid residues from a polypeptide of the present invention, wherein that number is selected from the group of integers consisting of from 10 to the number of residues in a full-length polypeptide of the present invention. Optionally, this subsequence of contiguous amino acids is at least 15, 20, 25, 30, 35, or 40 amino acids in length, often at least 50, 60, 70, 80, or 90 amino acids in length.
15 Further, the number of such subsequences can be any integer selected from the group consisting of from 1 to 20, such as 2, 3, 4, or 5.

- As those of skill will appreciate, the present invention includes catalytically active polypeptides of the present invention (i.e., enzymes). Catalytically active polypeptides have a specific activity of at least 20%, 30%, or 40%, and preferably at least 50%, 60%,
20 or 70%, and most preferably at least 80%, 90%, or 95% that of the native (non-synthetic), endogenous polypeptide. Further, the substrate specificity (k_{cat}/K_m) is optionally substantially similar to the native (non-synthetic), endogenous polypeptide. Typically, the K_m will be at least 30%, 40%, or 50%, that of the native (non-synthetic), endogenous polypeptide; and more preferably at least 60%, 70%, 80%, or 90%.
25 Methods of assaying and quantifying measures of enzymatic activity and substrate specificity (k_{cat}/K_m), are well known to those of skill in the art.

- Generally, the proteins of the present invention will, when presented as an immunogen, elicit production of an antibody specifically reactive to a polypeptide of the present invention. Further, the proteins of the present invention will not bind to antisera raised against a polypeptide of the present invention which has been fully immunosorbed with the same polypeptide. Immunoassays for determining binding are well known to those of skill in the art. A preferred immunoassay is a competitive immunoassay as discussed, *infra*. Thus, the proteins of the present invention can be employed as

immunogens for constructing antibodies immunoreactive to a protein of the present invention for such exemplary utilities as immunoassays or protein purification techniques.

5 **Expression of Proteins in Host Cells**

Using the nucleic acids of the present invention, one may express a protein of the present invention in a recombinantly engineered cell such as bacteria, yeast, insect, mammalian, or preferably plant cells. The cells produce the protein in a non-natural condition (e.g., in quantity, composition, location, and/or time), because they have been 10 genetically altered through human intervention to do so.

It is expected that those of skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a protein of the present invention. No attempt to describe in detail the various methods known for the expression of proteins in prokaryotes or eukaryotes will be made.

15 In brief summary, the expression of isolated nucleic acids encoding a protein of the present invention will typically be achieved by operably linking, for example, the DNA or cDNA to a promoter (which is either constitutive or inducible), followed by incorporation into an expression vector. The vectors can be suitable for replication and integration in either prokaryotes or eukaryotes. Typical expression vectors contain
20 transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the DNA encoding a protein of the present invention. To obtain high level expression of a cloned gene, it is desirable to construct expression vectors which contain, at the minimum, a strong promoter to direct transcription, a ribosome binding site for translational initiation, and a transcription/translation
25 terminator. One of skill would recognize that modifications can be made to a protein of the present invention without diminishing its biological activity. Some modifications may be made to facilitate the cloning, expression, or incorporation of the targeting molecule into a fusion protein. Such modifications are well known to those of skill in the art and include, for example, a methionine added at the amino terminus to provide an initiation site, or additional amino acids (e.g., poly His) placed on either terminus to create conveniently located purification sequences. Restriction sites or termination codons can also be introduced.
30

A. Expression in Prokaryotes

Prokaryotic cells may be used as hosts for expression. Prokaryotes most frequently are represented by various strains of *E. coli*; however, other microbial strains may also be used. Commonly used prokaryotic control sequences which are defined 5 herein to include promoters for transcription initiation, optionally with an operator, along with ribosome binding site sequences, include such commonly used promoters as the beta lactamase (penicillinase) and lactose (lac) promoter systems (Chang et al., *Nature* 198:1056 (1977)), the tryptophan (trp) promoter system (Goeddel et al., *Nucleic Acids Res.* 8:4057 (1980)) and the lambda derived P L promoter and N-gene ribosome 10 binding site (Shimatake et al., *Nature* 292:128 (1981)). The inclusion of selection markers in DNA vectors transfected in *E. coli* is also useful. Examples of such markers include genes specifying resistance to ampicillin, tetracycline, or chloramphenicol.

The vector is selected to allow introduction into the appropriate host cell. Bacterial vectors are typically of plasmid or phage origin. Appropriate bacterial cells are 15 infected with phage vector particles or transfected with naked phage vector DNA. If a plasmid vector is used, the bacterial cells are transfected with the plasmid vector DNA. Expression systems for expressing a protein of the present invention are available using *Bacillus sp.* and *Salmonella* (Palva, et al., *Gene* 22: 229-235 (1983); Mosbach, et al., *Nature* 302: 543-545 (1983)).

20

B. Expression in Eukaryotes

A variety of eukaryotic expression systems such as yeast, insect cell lines, plant and mammalian cells, are known to those of skill in the art. As explained briefly below, a 25 of the present invention can be expressed in these eukaryotic systems. In some embodiments, transformed/transfected plant cells, as discussed *infra*, are employed as expression systems for production of the proteins of the instant invention.

Synthesis of heterologous proteins in yeast is well known. Sherman, F., et al., *Methods in Yeast Genetics*, Cold Spring Harbor Laboratory (1982) is a well recognized work describing the various methods available to produce the protein in yeast. Two 30 widely utilized yeast for production of eukaryotic proteins are *Saccharomyces cerevisiae* and *Pichia pastoris*. Vectors, strains, and protocols for expression in *Saccharomyces* and *Pichia* are known in the art and available from commercial suppliers (e.g., Invitrogen). Suitable vectors usually have expression control sequences, such as

promoters, including 3-phosphoglycerate kinase or alcohol oxidase, and an origin of replication, termination sequences and the like as desired.

A protein of the present invention, once expressed, can be isolated from yeast by lysing the cells and applying standard protein isolation techniques to the lysates. The 5 monitoring of the purification process can be accomplished by using Western blot techniques or radioimmunoassay of other standard immunoassay techniques.

The sequences encoding proteins of the present invention can also be ligated to various expression vectors for use in transfecting cell cultures of, for instance, mammalian, insect, or plant origin. Illustrative of cell cultures useful for the production 10 of the peptides are mammalian cells. Mammalian cell systems often will be in the form of monolayers of cells although mammalian cell suspensions may also be used. A number of suitable host cell lines capable of expressing intact proteins have been developed in the art, and include the HEK293, BHK21, and CHO cell lines. Expression vectors for these cells can include expression control sequences, such as an origin of 15 replication, a promoter (*e.g.*, the CMV promoter, a HSV *tk* promoter or *pgk* (phosphoglycerate kinase) promoter), an enhancer (*Queen et al., Immunol. Rev.* 89: 49 (1986)), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites (*e.g.*, an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. Other animal cells useful for production of 20 proteins of the present invention are available, for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas (7th edition, 1992).

Appropriate vectors for expressing proteins of the present invention in insect cells are usually derived from the SF9 baculovirus. Suitable insect cell lines include mosquito larvae, silkworm, armyworm, moth and *Drosophila* cell lines such as a Schneider cell 25 line (See Schneider, *J. Embryol. Exp. Morphol.* 27: 353-365 (1987)).

As with yeast, when higher animal or plant host cells are employed, polyadenylation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenylation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript may also 30 be included. An example of a splicing sequence is the VP1 intron from SV40 (Sprague, *et al., J. Virol.* 45: 773-781 (1983)). Additionally, gene sequences to control replication in the host cell may be incorporated into the vector such as those found in bovine papilloma virus type-vectors. Saveria-Campo, M., Bovine Papilloma Virus DNA a

Eukaryotic Cloning Vector in *DNA Cloning Vol. II a Practical Approach*, D.M. Glover, Ed., IRL Press, Arlington, Virginia pp. 213-238 (1985).

Transfection/Transformation of Cells

- 5 The method of transformation/transfection is not critical to the instant invention; various methods of transformation or transfection are currently available. As newer methods are available to transform crops or other host cells they may be directly applied. Accordingly, a wide variety of methods have been developed to insert a DNA sequence into the genome of a host cell to obtain the transcription and/or translation of the
10 sequence to effect phenotypic changes in the organism. Thus, any method which provides for efficient transformation/transfection may be employed.

A. Plant Transformation

- A DNA sequence coding for the desired polynucleotide of the present invention,
15 for example a cDNA or a genomic sequence encoding a full length protein, will be used to construct a recombinant expression cassette which can be introduced into the desired plant.

- Isolated nucleic acid acids of the present invention can be introduced into plants according techniques known in the art. Generally, recombinant expression cassettes as
20 described above and suitable for transformation of plant cells are prepared. Techniques for transforming a wide variety of higher plant species are well known and described in the technical, scientific, and patent literature. See, for example, Weising *et al.*, *Ann. Rev. Genet.* 22: 421-477 (1988). For example, the DNA construct may be introduced directly into the genomic DNA of the plant cell using techniques such as electroporation,
25 PEG poration, particle bombardment, silicon fiber delivery, or microinjection of plant cell protoplasts or embryogenic callus. See e.g., Tomes, *et al.*, *Direct DNA Transfer into Intact Plant Cells via Microprojectile Bombardment*, pp. 197-213 in *Plant Cell, Tissue and Organ Culture, Fundamental Methods*, (eds. O.L. Gamborg and G.C. Phillips, Springer-Verlag Berlin Heidelberg New York, 1995). Alternatively, the DNA
30 constructs may be combined with suitable T-DNA flanking regions and introduced into a conventional *Agrobacterium tumefaciens* host vector. The virulence functions of the *Agrobacterium tumefaciens* host will direct the insertion of the construct and adjacent

marker into the plant cell DNA when the cell is infected by the bacteria. See, U.S. Patent No. 5,591,616.

The introduction of DNA constructs using polyethylene glycol precipitation is described in Paszkowski *et al.*, *Embo J.* 3: 2717-2722 (1984). Electroporation techniques are described in Fromm *et al.*, *Proc. Natl. Acad. Sci.* 82: 5824 (1985). Ballistic transformation techniques are described in Klein *et al.*, *Nature* 327: 70-73 (1987).

Agrobacterium tumefaciens-mediated transformation techniques are well described in the scientific literature. See, for example Horsch *et al.*, *Science* 233: 496-498 (1984), and Fraley *et al.*, *Proc. Natl. Acad. Sci.* 80: 4803 (1983). Although *Agrobacterium* is useful primarily in dicots, certain monocots can be transformed by *Agrobacterium*. For instance, *Agrobacterium* transformation of maize is described in U.S. Patent No. 5,550,318.

Other methods of transfection or transformation include (1) *Agrobacterium rhizogenes*-mediated transformation (see, e.g., Lichtenstein and Fuller In: *Genetic Engineering*, vol. 6, PWJ Rigby, Ed., London, Academic Press, 1987; and Lichtenstein, C. P., and Draper, J., In: *DNA Cloning*, Vol. II, D. M. Glover, Ed., Oxford, IRI Press, 1985), Application PCT/US87/02512 (WO 88/02405 published Apr. 7, 1988) describes the use of *A. rhizogenes* strain A4 and its Ri plasmid along with *A. tumefaciens* vectors pARC8 or pARC16 (2) liposome-mediated DNA uptake (see, e.g., Freeman *et al.*, *Plant Cell Physiol.* 25: 1353, 1984), (3) the vortexing method (see, e.g., Kindle, *Proc. Natl. Acad. Sci.*, USA 87: 1228, (1990)).

DNA can also be introduced into plants by direct DNA transfer into pollen as described by Zhou *et al.*, *Methods in Enzymology*, 101:433 (1983); D. Hess, *Intern Rev. Cytol.*, 107:367 (1987); Luo *et al.*, *Plane Mol. Biol. Reporter*, 6:165 (1988). Expression of polypeptide coding genes can be obtained by injection of the DNA into reproductive organs of a plant as described by Pena *et al.*, *Nature*, 325.:274 (1987). DNA can also be injected directly into the cells of immature embryos and the rehydration of desiccated embryos as described by Neuhaus *et al.*, *Theor. Appl. Genet.*, 75:30 (1987); and Benbrook *et al.*, in *Proceedings Bio Expo 1986*, Butterworth, Stoneham, Mass., pp. 27-54 (1986). A variety of plant viruses that can be employed as vectors are known in the art and include cauliflower mosaic virus (CaMV), geminivirus, brome mosaic virus, and tobacco mosaic virus.

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B. Transfection of Prokaryotes, Lower Eukaryotes, and Animal Cells

Animal and lower eukaryotic (e.g., yeast) host cells are competent or rendered competent for transfection by various means. There are several well-known methods of introducing DNA into animal cells. These include: calcium phosphate precipitation, 5 fusion of the recipient cells with bacterial protoplasts containing the DNA, treatment of the recipient cells with liposomes containing the DNA, DEAE dextran, electroporation, biolistics, and micro-injection of the DNA directly into the cells. The transfected cells are cultured by means well known in the art. Kuchler, R.J., *Biochemical Methods in Cell Culture and Virology*, Dowden, Hutchinson and Ross, Inc. (1977).

10

Synthesis of Proteins

The proteins of the present invention can be constructed using non-cellular synthetic methods. Solid phase synthesis of proteins of less than about 50 amino acids in length may be accomplished by attaching the C-terminal amino acid of the sequence to an 15 insoluble support followed by sequential addition of the remaining amino acids in the sequence. Techniques for solid phase synthesis are described by Barany and Merrifield, Solid-Phase Peptide Synthesis, pp. 3-284 in *The Peptides: Analysis, Synthesis, Biology*. Vol. 2: *Special Methods in Peptide Synthesis, Part A.*; Merrifield, et al., *J. Am. Chem. Soc.* 85: 2149-2156 (1963), and Stewart et al., *Solid Phase Peptide Synthesis*, 2nd ed., 20 Pierce Chem. Co., Rockford, Ill. (1984). Proteins of greater length may be synthesized by condensation of the amino and carboxy termini of shorter fragments. Methods of forming peptide bonds by activation of a carboxy terminal end (e.g., by the use of the coupling reagent N,N'-dicyclohexylcarbodiimide)) is known to those of skill.

25 **Purification of Proteins**

The proteins of the present invention may be purified by standard techniques well known to those of skill in the art. Recombinantly produced proteins of the present invention can be directly expressed or expressed as a fusion protein. The recombinant protein is purified by a combination of cell lysis (e.g., sonication, French press) and 30 affinity chromatography. For fusion products, subsequent digestion of the fusion protein with an appropriate proteolytic enzyme releases the desired recombinant protein.

The proteins of this invention, recombinant or synthetic, may be purified to substantial purity by standard techniques well known in the art, including detergent

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solubilization, selective precipitation with such substances as ammonium sulfate, column chromatography, immunopurification methods, and others. See, for instance, R. Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag: New York (1982); Deutscher, *Guide to Protein Purification*, Academic Press (1990). For example,

5 antibodies may be raised to the proteins as described herein. Purification from *E. coli* can be achieved following procedures described in U.S. Patent No. 4,511,503. The protein may then be isolated from cells expressing the protein and further purified by standard protein chemistry techniques as described herein. Detection of the expressed protein is achieved by methods known in the art and include, for example,

10 radioimmunoassays, Western blotting techniques or immunoprecipitation.

Transgenic Plant Regeneration

Transformed plant cells which are derived by any of the above transformation techniques can be cultured to regenerate a whole plant which possesses the transformed genotype. Such regeneration techniques often rely on manipulation of certain phytohormones in a tissue culture growth medium, typically relying on a biocide and/or herbicide marker which has been introduced together with a polynucleotide of the present invention. For transformation and regeneration of maize see, Gordon-Kamm *et al.*, *The Plant Cell*, 2:603-618 (1990).

20 Plants cells transformed with a plant expression vector can be regenerated, e.g., from single cells, callus tissue or leaf discs according to standard plant tissue culture techniques. It is well known in the art that various cells, tissues, and organs from almost any plant can be successfully cultured to regenerate an entire plant. Plant regeneration from cultured protoplasts is described in Evans *et al.*, *Protoplasts Isolation and Culture*,
15 *Handbook of Plant Cell Culture*, Macmillan Publishing Company, New York, pp. 124-176 (1983); and Binding, *Regeneration of Plants, Plant Protoplasts*, CRC Press, Boca Raton, pp. 21-73 (1985).

The regeneration of plants containing the foreign gene introduced by *Agrobacterium* from leaf explants can be achieved as described by Horsch *et al.*,
30 *Science*, 227:1229-1231 (1985). In this procedure, transformants are grown in the presence of a selection agent and in a medium that induces the regeneration of shoots in the plant species being transformed as described by Fraley *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 80:4803 (1983). This procedure typically produces shoots within two to four

weeks and these transformant shoots are then transferred to an appropriate root-inducing medium containing the selective agent and an antibiotic to prevent bacterial growth.

Transgenic plants of the present invention may be fertile or sterile.

Regeneration can also be obtained from plant callus, explants, organs, or parts thereof. Such regeneration techniques are described generally in Klee *et al.*, *Ann. Rev. of Plant Phys.* 38: 467-486 (1987). The regeneration of plants from either single plant protoplasts or various explants is well known in the art. See, for example, *Methods for Plant Molecular Biology*, A. Weissbach and H. Weissbach, eds., Academic Press, Inc., San Diego, Calif. (1988). This regeneration and growth process includes the steps of selection of transformant cells and shoots, rooting the transformant shoots and growth of the plantlets in soil. For maize cell culture and regeneration see generally, *The Maize Handbook*, Freeling and Walbot, Eds., Springer, New York (1994); *Corn and Corn Improvement*, 3rd edition, Sprague and Dudley Eds., American Society of Agronomy, Madison, Wisconsin (1988).

One of skill will recognize that after the recombinant expression cassette is stably incorporated in transgenic plants and confirmed to be operable, it can be introduced into other plants by sexual crossing. Any of a number of standard breeding techniques can be used, depending upon the species to be crossed.

In vegetatively propagated crops, mature transgenic plants can be propagated by the taking of cuttings or by tissue culture techniques to produce multiple identical plants. Selection of desirable transgenics is made and new varieties are obtained and propagated vegetatively for commercial use. In seed propagated crops, mature transgenic plants can be self crossed to produce a homozygous inbred plant. The inbred plant produces seed containing the newly introduced heterologous nucleic acid. These seeds can be grown to produce plants that would produce the selected phenotype.

Parts obtained from the regenerated plant, such as flowers, seeds, leaves, branches, fruit, and the like are included in the invention, provided that these parts comprise cells comprising the isolated nucleic acid of the present invention. Progeny and variants, and mutants of the regenerated plants are also included within the scope of the invention, provided that these parts comprise the introduced nucleic acid sequences.

Transgenic plants expressing the selectable marker can be screened for transmission of the nucleic acid of the present invention by, for example, standard immunoblot and DNA detection techniques. Transgenic lines are also typically evaluated

on levels of expression of the heterologous nucleic acid. Expression at the RNA level can be determined initially to identify and quantitate expression-positive plants. Standard techniques for RNA analysis can be employed and include PCR amplification assays using oligonucleotide primers designed to amplify only the heterologous RNA templates 5 and solution hybridization assays using heterologous nucleic acid-specific probes. The RNA-positive plants can then analyzed for protein expression by Western immunoblot analysis using the specifically reactive antibodies of the present invention. In addition, *in situ* hybridization and immunocytochemistry according to standard protocols can be done using heterologous nucleic acid specific polynucleotide probes and antibodies, 10 respectively, to localize sites of expression within transgenic tissue. Generally, a number of transgenic lines are usually screened for the incorporated nucleic acid to identify and select plants with the most appropriate expression profiles.

A preferred embodiment is a transgenic plant that is homozygous for the added heterologous nucleic acid; i.e., a transgenic plant that contains two added nucleic acid 15 sequences, one gene at the same locus on each chromosome of a chromosome pair. A homozygous transgenic plant can be obtained by sexually mating (selfing) a heterozygous transgenic plant that contains a single added heterologous nucleic acid, germinating some of the seed produced and analyzing the resulting plants produced for altered expression of a polynucleotide of the present invention relative to a control plant (i.e., native, non- 20 transgenic). Back-crossing to a parental plant and out-crossing with a non-transgenic plant are also contemplated.

Modulating Polypeptide Levels and/or Composition

The present invention further provides a method for modulating (i.e., increasing 25 or decreasing) the concentration or composition of the polypeptides of the present invention in a plant or part thereof. Modulation can be effected by increasing or decreasing the concentration and/or the composition (i.e., the ratio of the polypeptides of the present invention) in a plant. The method comprises transforming a plant cell with a recombinant expression cassette comprising a polynucleotide of the present invention as 30 described above to obtain a transformed plant cell, growing the transformed plant cell under plant forming conditions, and inducing expression of a polynucleotide of the present invention in the plant for a time sufficient to modulate concentration and/or composition in the plant or plant part.

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In some embodiments, the content and/or composition of polypeptides of the present invention in a plant may be modulated by altering, *in vivo* or *in vitro*, the promoter of a non-isolated gene of the present invention to up- or down-regulate gene expression. In some embodiments, the coding regions of native genes of the present invention can be altered via substitution, addition, insertion, or deletion to decrease activity of the encoded enzyme. See, e.g., Kmiec, U.S. Patent 5,565,350; Zarling *et al.*, PCT/US93/03868. And in some embodiments, an isolated nucleic acid (e.g., a vector) comprising a promoter sequence is transfected into a plant cell. Subsequently, a plant cell comprising the promoter operably linked to a polynucleotide of the present invention is selected for by means known to those of skill in the art such as, but not limited to, Southern blot, DNA sequencing, or PCR analysis using primers specific to the promoter and to the gene and detecting amplicons produced therefrom. A plant or plant part altered or modified by the foregoing embodiments is grown under plant forming conditions for a time sufficient to modulate the concentration and/or composition of polypeptides of the present invention in the plant. Plant forming conditions are well known in the art and discussed briefly, *above*.

- In general, concentration or composition is increased or decreased by at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% relative to a native control plant, plant part, or cell lacking the aforementioned recombinant expression cassette.
- Modulation in the present invention may occur during and/or subsequent to growth of the plant to the desired stage of development. Modulating nucleic acid expression temporally and/or in particular tissues can be controlled by employing the appropriate promoter operably linked to a polynucleotide of the present invention in, for example, sense or antisense orientation as discussed in greater detail, *above*. Induction of expression of a polynucleotide of the present invention can also be controlled by exogenous administration of an effective amount of inducing compound. Inducible promoters and inducing compounds which activate expression from these promoters are well known in the art. In preferred embodiments, the polypeptides of the present invention are modulated in monocots, particularly maize.

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The present invention provides a method of genotyping a plant comprising a polynucleotide of the present invention. Preferably, the plant is a monocot, such as maize or sorghum. Genotyping provides a means of distinguishing homologs of a chromosome pair and can be used to differentiate segregants in a plant population.

- 5 Molecular marker methods can be used for phylogenetic studies, characterizing genetic relationships among crop varieties, identifying crosses or somatic hybrids, localizing chromosomal segments affecting monogenic traits, map based cloning, and the study of quantitative inheritance. See, e.g., *Plant Molecular Biology: A Laboratory Manual*, Chapter 7, Clark, Ed., Springer-Verlag, Berlin (1997). For molecular marker methods,
- 10 see generally, *The DNA Revolution* by Andrew H. Paterson 1996 (Chapter 2) in: *Genome Mapping in Plants* (ed. Andrew H. Paterson) by Academic Press/R. G. Landis Company, Austin, Texas, pp.7-21.

The particular method of genotyping in the present invention may employ any number of molecular marker analytic techniques such as, but not limited to, restriction fragment length polymorphisms (RFLPs). RFLPs are the product of allelic differences between DNA restriction fragments caused by nucleotide sequence variability. As is well known to those of skill in the art, RFLPs are typically detected by extraction of genomic DNA and digestion with a restriction enzyme. Generally, the resulting fragments are separated according to size and hybridized with a probe; single copy probes are preferred. Restriction fragments from homologous chromosomes are revealed. Differences in fragment size among alleles represent an RFLP. Thus, the present invention further provides a means to follow segregation of a gene or nucleic acid of the present invention as well as chromosomal sequences genetically linked to these genes or nucleic acids using such techniques as RFLP analysis. Linked chromosomal sequences are within 50 centiMorgans (cM), often within 40 or 30 cM, preferably within 20 or 10 cM, more preferably within 5, 3, 2, or 1 cM of a gene of the present invention.

In the present invention, the nucleic acid probes employed for molecular marker mapping of plant nuclear genomes selectively hybridize, under selective hybridization conditions, to a gene encoding a polynucleotide of the present invention. In preferred embodiments, the probes are selected from polynucleotides of the present invention. Typically, these probes are cDNA probes or *Pst I* genomic clones. The length of the probes is discussed in greater detail, above, but are typically at least 15 bases in length,

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more preferably at least 20, 25, 30, 35, 40, or 50 bases in length. Generally, however, the probes are less than about 1 kilobase in length. Preferably, the probes are single copy probes that hybridize to a unique locus in a haploid chromosome complement. Some exemplary restriction enzymes employed in RFLP mapping are *EcoRI*, *EcoRV*, and 5 *SstI*. As used herein the term "restriction enzyme" includes reference to a composition that recognizes and, alone or in conjunction with another composition, cleaves at a specific nucleotide sequence.

The method of detecting an RFLP comprises the steps of (a) digesting genomic DNA of a plant with a restriction enzyme; (b) hybridizing a nucleic acid probe, under 10 selective hybridization conditions, to a sequence of a polynucleotide of the present of said genomic DNA; (c) detecting therefrom a RFLP. Other methods of differentiating polymorphic (allelic) variants of polynucleotides of the present invention can be had by utilizing molecular marker techniques well known to those of skill in the art including such techniques as: 1) single stranded conformation analysis (SSCP); 2) denaturing 15 gradient gel electrophoresis (DGGE); 3) RNase protection assays; 4) allele-specific oligonucleotides (ASOs); 5) the use of proteins which recognize nucleotide mismatches, such as the *E. coli* mutS protein; and 6) allele-specific PCR. Other approaches based on the detection of mismatches between the two complementary DNA strands include clamped denaturing gel electrophoresis (CDGE); heteroduplex analysis (HA); and 20 chemical mismatch cleavage (CMC). Exemplary polymorphic variants are provided in Table I, above. Thus, the present invention further provides a method of genotyping comprising the steps of contacting, under stringent hybridization conditions, a sample suspected of comprising a polynucleotide of the present invention with a nucleic acid probe. Generally, the sample is a plant sample; preferably, a sample suspected of 25 comprising a maize polynucleotide of the present invention (e.g., gene, mRNA). The nucleic acid probe selectively hybridizes, under stringent conditions, to a subsequence of a polynucleotide of the present invention comprising a polymorphic marker. Selective hybridization of the nucleic acid probe to the polymorphic marker nucleic acid sequence yields a hybridization complex. Detection of the hybridization complex indicates the 30 presence of that polymorphic marker in the sample. In preferred embodiments, the nucleic acid probe comprises a polynucleotide of the present invention.

UTR's and Codon Preference

In general, translational efficiency has been found to be regulated by specific sequence elements in the 5' non-coding or untranslated region (5' UTR) of the RNA. Positive sequence motifs include translational initiation consensus sequences (Kozak, *Nucleic Acids Res.* 15:8125 (1987)) and the 7-methylguanosine cap structure (Drummond *et al.*, *Nucleic Acids Res.* 13:7375 (1985)). Negative elements include stable intramolecular 5' UTR stem-loop structures (Muesing *et al.*, *Cell* 48:691 (1987)) and AUG sequences or short open reading frames preceded by an appropriate AUG in the 5' UTR (Kozak, above, Rao *et al.*, *Mol. and Cell. Biol.* 8:284 (1988)). Accordingly, the present invention provides 5' and/or 3' UTR regions for modulation of translation of heterologous coding sequences.

Further, the polypeptide-encoding segments of the polynucleotides of the present invention can be modified to alter codon usage. Altered codon usage can be employed to alter translational efficiency and/or to optimize the coding sequence for expression in a desired host or to optimize the codon usage in a heterologous sequence for expression in maize. Codon usage in the coding regions of the polynucleotides of the present invention can be analyzed statistically using commercially available software packages such as "Codon Preference" available from the University of Wisconsin Genetics Computer Group (see Devereaux *et al.*, *Nucleic Acids Res.* 12: 387-395 (1984)) or MacVector 4.1 (Eastman Kodak Co., New Haven, Conn.). Thus, the present invention provides a codon usage frequency characteristic of the coding region of at least one of the polynucleotides of the present invention. The number of polynucleotides that can be used to determine a codon usage frequency can be any integer from 1 to the number of polynucleotides of the present invention as provided herein. Optionally, the polynucleotides will be full-length sequences. An exemplary number of sequences for statistical analysis can be at least 1, 5, 10, 20, 50, or 100.

Sequence Shuffling

The present invention provides methods for sequence shuffling using polynucleotides of the present invention, and compositions resulting therefrom.

Sequence shuffling is described in PCT publication No. 96/19256. See also, Zhang, J.-H., *et al. Proc. Natl. Acad. Sci. USA* 94:4504-4509 (1997). Generally, sequence shuffling provides a means for generating libraries of polynucleotides having a desired characteristic which can be selected or screened for. Libraries of recombinant

polynucleotides are generated from a population of related sequence polynucleotides which comprise sequence regions which have substantial sequence identity and can be homologously recombined in vitro or in vivo. The population of sequence-recombined polynucleotides comprises a subpopulation of polynucleotides which possess desired or 5 advantageous characteristics and which can be selected by a suitable selection or screening method. The characteristics can be any property or attribute capable of being selected for or detected in a screening system, and may include properties of: an encoded protein, a transcriptional element, a sequence controlling transcription, RNA processing, RNA stability, chromatin conformation, translation, or other expression property of a 10 gene or transgene, a replicative element, a protein-binding element, or the like, such as any feature which confers a selectable or detectable property. In some embodiments, the selected characteristic will be a decreased K_m and/or increased K_{cat} over the wild-type protein as provided herein. In other embodiments, a protein or polynucleotide generated from sequence shuffling will have a ligand binding affinity greater than the non-shuffled 15 wild-type polynucleotide. The increase in such properties can be at least 110%, 120%, 130%, 140% or at least 150% of the wild-type value.

Generic and Consensus Sequences

Polynucleotides and polypeptides of the present invention further include those 20 having: (a) a generic sequence of at least two homologous polynucleotides or polypeptides, respectively, of the present invention; and, (b) a consensus sequence of at least three homologous polynucleotides or polypeptides, respectively, of the present invention. The generic sequence of the present invention comprises each species of polypeptide or polynucleotide embraced by the generic polypeptide or polynucleotide, 25 sequence, respectively. The individual species encompassed by a polynucleotide having an amino acid or nucleic acid consensus sequence can be used to generate antibodies or produce nucleic acid probes or primers to screen for homologs in other species, genera, families, orders, classes, phyla, or kingdoms. For example, a polynucleotide having a consensus sequences from a gene family of *Zea mays* can be used to generate antibody or 30 nucleic acid probes or primers to other *Gramineae* species such as wheat, rice, or sorghum. Alternatively, a polynucleotide having a consensus sequence generated from orthologous genes can be used to identify or isolate orthologs of other taxa. Typically, a polynucleotide having a consensus sequence will be at least 9, 10, 15, 20, 25, 30, or 40

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amino acids in length, or 20, 30, 40, 50, 100, or 150 nucleotides in length. As those of skill in the art are aware, a conservative amino acid substitution can be used for amino acids which differ amongst aligned sequence but are from the same conservative substitution group as discussed above. Optionally, no more than 1 or 2 conservative 5 amino acids are substituted for each 10 amino acid length of consensus sequence.

Similar sequences used for generation of a consensus or generic sequence include any number and combination of allelic variants of the same gene, orthologous, or paralogous sequences as provided herein. Optionally, similar sequences used in generating a consensus or generic sequence are identified using the BLAST algorithm's 10 smallest sum probability ($P(N)$). Various suppliers of sequence-analysis software are listed in chapter 7 of *Current Protocols in Molecular Biology*, F.M. Ausubel *et al.*, Eds., Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc. (Supplement 30). A polynucleotide sequence is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic 15 acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, or 0.001, and most preferably less than about 0.0001, or 0.00001. Similar polynucleotides can be aligned and a consensus or generic sequence generated using multiple sequence alignment software available from a number of commercial suppliers such as the Genetics Computer Group's (Madison, WI) PILEUP software, Vector NTT's 20 (North Bethesda, MD) ALIGNX, or Genecode's (Ann Arbor, MI) SEQUENCHER. Conveniently, default parameters of such software can be used to generate consensus or generic sequences.

Detection of Nucleic Acids

25 The present invention further provides methods for detecting a polynucleotide of the present invention in a nucleic acid sample suspected of comprising a polynucleotide of the present invention, such as a plant cell lysate, particularly a lysate of corn. In some embodiments, a gene of the present invention or portion thereof can be amplified prior to the step of contacting the nucleic acid sample with a polynucleotide of the 30 present invention. The nucleic acid sample is contacted with the polynucleotide to form a hybridization complex. The polynucleotide hybridizes under stringent conditions to a gene encoding a polypeptide of the present invention. Formation of the hybridization complex is used to detect a gene encoding a polypeptide of the present invention in the

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nucleic acid sample. Those of skill will appreciate that an isolated nucleic acid comprising a polynucleotide of the present invention should lack cross-hybridizing sequences in common with non-target genes that would yield a false positive result.

Detection of the hybridization complex can be achieved using any number of well known methods. For example, the nucleic acid sample, or a portion thereof, may be assayed by hybridization formats including but not limited to, solution phase, solid phase, mixed phase, or *in situ* hybridization assays. Briefly, in solution (or liquid) phase hybridizations, both the target nucleic acid and the probe or primer are free to interact in the reaction mixture. In solid phase hybridization assays, probes or primers are typically linked to a solid support where they are available for hybridization with target nucleic in solution. In mixed phase, nucleic acid intermediates in solution hybridize to target nucleic acids in solution as well as to a nucleic acid linked to a solid support. In *in situ* hybridization, the target nucleic acid is liberated from its cellular surroundings in such as to be available for hybridization within the cell while preserving the cellular morphology for subsequent interpretation and analysis. The following articles provide an overview of the various hybridization assay formats: Singer *et al.*, *Biotechniques* 4(3): 230-250 (1986); Haase *et al.*, *Methods in Virology*, Vol. VII, pp. 189-226 (1984); Wilkinson, The theory and practice of *in situ* hybridization in: *In situ Hybridization*, D.G. Wilkinson, Ed., IRL Press, Oxford University Press, Oxford; and *Nucleic Acid Hybridization: A Practical Approach*, Hames, B.D. and Higgins, S.J., Eds., IRL Press (1987).

Nucleic Acid Labels and Detection Methods

The means by which nucleic acids of the present invention are labeled is not a critical aspect of the present invention and can be accomplished by any number of methods currently known or later developed. Detectable labels suitable for use in the present invention include any composition detectable by spectroscopic, radioisotopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate, magnetic beads, fluorescent dyes (*e.g.*, fluorescein, texas red, rhodamine, green fluorescent protein, and the like), radiolabels (*e.g.*, ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P), enzymes (*e.g.*, horse radish peroxidase, alkaline phosphatase and others commonly used

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in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads.

Nucleic acids of the present invention can be labeled by any one of several methods typically used to detect the presence of hybridized nucleic acids. One common method of detection is the use of autoradiography using probes labeled with ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P , or the like. The choice of radio-active isotope depends on research preferences due to ease of synthesis, stability, and half lives of the selected isotopes. Other labels include ligands which bind to antibodies labeled with fluorophores, chemiluminescent agents, and enzymes. Alternatively, probes can be conjugated directly with labels such as fluorophores, chemiluminescent agents or enzymes. The choice of label depends on sensitivity required, ease of conjugation with the probe, stability requirements, and available instrumentation. Labeling the nucleic acids of the present invention is readily achieved such as by the use of labeled PCR primers.

In some embodiments, the label is simultaneously incorporated during the amplification step in the preparation of the nucleic acids. Thus, for example, polymerase chain reaction (PCR) with labeled primers or labeled nucleotides will provide a labeled amplification product. In another embodiment, transcription amplification using a labeled nucleotide (e.g., fluorescein-labeled UTP and/or CTP) incorporates a label into the transcribed nucleic acids.

Non-radioactive probes are often labeled by indirect means. For example, a ligand molecule is covalently bound to the probe. The ligand then binds to an anti-ligand molecule which is either inherently detectable or covalently bound to a detectable signal system, such as an enzyme, a fluorophore, or a chemiluminescent compound. Enzymes of interest as labels will primarily be hydrolases, such as phosphatases, esterases and glycosidases, or oxidoreductases, particularly peroxidases. Fluorescent compounds include fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, etc. Chemiluminescers include luciferin, and 2,3-dihydrophthalazinediones, e.g., luminol. Ligands and anti-ligands may be varied widely. Where a ligand has a natural anti-ligand, namely ligands such as biotin, thyroxine, and cortisol, it can be used in conjunction with its labeled, naturally occurring anti-ligands. Alternatively, any haptenic or antigenic compound can be used in combination with an antibody.

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- Probes can also be labeled by direct conjugation with a label. For example, cloned DNA probes have been coupled directly to horseradish peroxidase or alkaline phosphatase, (Renz, M., and Kurz, K., *A Colorimetric Method for DNA Hybridization*, *Nucl. Acids Res.* 12: 3435-3444 (1984)) and synthetic oligonucleotides have been
5 coupled directly with alkaline phosphatase (Jablonski, E., et al., *Preparation of Oligodeoxynucleotide-Alkaline Phosphatase Conjugates and Their Use as Hybridization Probes*, *Nuc. Acids. Res.* 14: 6115-6128 (1986); and Li P., et al., *Enzyme-linked Synthetic Oligonucleotide probes: Non-Radioactive Detection of Enterotoxigenic Escherichia Coli in Faecal Specimens*, *Nucl. Acids Res.* 15: 5275-5287 (1987)).
10 Means of detecting such labels are well known to those of skill in the art. Thus, for example, radiolabels may be detected using photographic film or scintillation counters, fluorescent markers may be detected using a photodetector to detect emitted light. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting the reaction product produced by the action of the enzyme on the substrate,
15 and colorimetric labels are detected by simply visualizing the colored label.

Antibodies to Proteins

- Antibodies can be raised to a protein of the present invention, including individual, allelic, strain, or species variants, and fragments thereof, both in their naturally occurring (full-length) forms and in recombinant forms. Additionally, antibodies are raised to these proteins in either their native configurations or in non-native configurations. Anti-idiotypic antibodies can also be generated. Many methods of making antibodies are known to persons of skill. The following discussion is presented as a general overview of the techniques available; however, one of skill will
20 recognize that many variations upon the following methods are known.
25

- A number of immunogens are used to produce antibodies specifically reactive with a protein of the present invention. An isolated recombinant, synthetic, or native polynucleotide of the present invention are the preferred immunogens (antigen) for the production of monoclonal or polyclonal antibodies. Those of skill will readily
30 understand that the proteins of the present invention are typically denatured, and optionally reduced, prior to formation of antibodies for screening expression libraries or other assays in which a putative protein of the present invention is expressed or

denatured in a non-native secondary, tertiary, or quartenary structure. Non-isolated polypeptides of the present invention can be used either in pure or impure form.

The protein of the present invention is then injected into an animal capable of producing antibodies. Either monoclonal or polyclonal antibodies can be generated for 5 subsequent use in immunoassays to measure the presence and quantity of the protein of the present invention. Methods of producing polyclonal antibodies are known to those of skill in the art. In brief, an immunogen (antigen), preferably a purified protein, a protein coupled to an appropriate carrier (*e.g.*, GST, keyhole limpet hemocyanin, *etc.*), or a protein incorporated into an immunization vector such as a recombinant vaccinia virus 10 (*see*, U.S. Patent No. 4,722,848) is mixed with an adjuvant and animals are immunized with the mixture. The animal's immune response to the immunogen preparation is monitored by taking test bleeds and determining the titer of reactivity to the protein of interest. When appropriately high titers of antibody to the immunogen are obtained, blood is collected from the animal and antisera are prepared. Further fractionation of the 15 antisera to enrich for antibodies reactive to the protein is performed where desired (*See*, *e.g.*, Coligan, *Current Protocols in Immunology*, Wiley/Greene, NY (1991); and Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press, NY (1989)).

Antibodies, including binding fragments and single chain recombinant versions thereof, against predetermined fragments of a protein of the present invention are raised 20 by immunizing animals, *e.g.*, with conjugates of the fragments with carrier proteins as described above. Typically, the immunogen of interest is a protein of at least about 5 amino acids, more typically the protein is 10 amino acids in length, preferably, 15 amino acids in length and more preferably the protein is 20 amino acids in length or greater. The peptides are typically coupled to a carrier protein (*e.g.*, as a fusion protein), or are 25 recombinantly expressed in an immunization vector. Antigenic determinants on peptides to which antibodies bind are typically 3 to 10 amino acids in length.

Monoclonal antibodies are prepared from cells secreting the desired antibody. Monoclonals antibodies are screened for binding to a protein from which the immunogen was derived. Specific monoclonal and polyclonal antibodies will usually have an 30 antibody binding site with an affinity constant for its cognate monovalent antigen at least between 10^6 - 10^7 , usually at least 10^8 , preferably at least 10^9 , more preferably at least 10^{10} , and most preferably at least 10^{11} liters/mole.

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In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies are found in, e.g., *Basic and Clinical Immunology*, 4th ed., Stites *et al.*, Eds., Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane, *Supra*; Goding, *Monoclonal Antibodies: Principles and Practice*, 2nd ed., Academic Press, New York, NY (1986); and Kohler and Milstein, *Nature* 256: 495-497 (1975). Summarized briefly, this method proceeds by injecting an animal with an immunogen comprising a protein of the present invention. The animal is then sacrificed and cells taken from its spleen, which are fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing *in vitro*. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve selection of libraries of recombinant antibodies in phage or similar vectors (see, e.g., Huse *et al.*, *Science* 246: 1275-1281 (1989); and Ward, *et al.*, *Nature* 341: 544-546 (1989); and Vaughan *et al.*, *Nature Biotechnology*, 14: 309-314 (1996)). Alternatively, high avidity human monoclonal antibodies can be obtained from transgenic mice comprising fragments of the unarranged human heavy and light chain Ig loci (i.e., minilocus transgenic mice). Fishwild *et al.*, *Nature Biotech.*, 14: 845-851 (1996). Also, recombinant immunoglobulins may be produced. See, Cabilly, U.S. Patent No. 4,816,567; and Queen *et al.*, *Proc. Nat'l Acad. Sci.* 86: 10029-10033 (1989).

The antibodies of this invention are also used for affinity chromatography in isolating proteins of the present invention. Columns are prepared, e.g., with the antibodies linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where a cell lysate is passed through the column, washed, and treated with increasing concentrations of a mild denaturant, whereby purified protein are released.

The antibodies can be used to screen expression libraries for particular expression products such as normal or abnormal protein. Usually the antibodies in such a procedure are labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

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Antibodies raised against a protein of the present invention can also be used to raise anti-idiotypic antibodies. These are useful for detecting or diagnosing various pathological conditions related to the presence of the respective antigens.

Frequently, the proteins and antibodies of the present invention will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionucleotides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like.

10

Protein Immunoassays

Means of detecting the proteins of the present invention are not critical aspects of the present invention. In a preferred embodiment, the proteins are detected and/or quantified using any of a number of well recognized immunological binding assays (see, e.g., U.S. Patents 4,366,241; 4,376,110; 4,517,288; and 4,837,168). For a review of the general immunoassays, see also *Methods in Cell Biology*, Vol. 37: *Antibodies in Cell Biology*, Asai, Ed., Academic Press, Inc. New York (1993); *Basic and Clinical Immunology* 7th Edition, Stites & Terr, Eds. (1991). Moreover, the immunoassays of the present invention can be performed in any of several configurations, e.g., those reviewed in *Enzyme Immunoassay*, Maggio, Ed., CRC Press, Boca Raton, Florida (1980); Tijan, *Practice and Theory of Enzyme Immunoassays, Laboratory Techniques in Biochemistry and Molecular Biology*, Elsevier Science Publishers B.V., Amsterdam (1985); Harlow and Lane, above; *Immunoassay: A Practical Guide*, Chan, Ed., Academic Press, Orlando, FL (1987); *Principles and Practice of Immunoassays*, Price and Newman Eds., Stockton Press, NY (1991); and *Non-isotopic Immunoassays*, Ngo, Ed., Plenum Press, NY (1988). Immunological binding assays (or immunoassays) typically utilize a "capture agent" to specifically bind to and often immobilize the analyte (in this case, a protein of the present invention). The capture agent is a moiety that specifically binds to the analyte. In a preferred embodiment, the capture agent is an antibody that specifically binds a protein(s) of the present invention. The antibody may be produced by any of a number of means known to those of skill in the art as described herein.

Immunoassays also often utilize a labeling agent to specifically bind to and label the binding complex formed by the capture agent and the analyte. The labeling agent may itself be one of the moieties comprising the antibody/analyte complex. Thus, the labeling agent may be a labeled protein of the present invention or a labeled antibody 5 specifically reactive to a protein of the present invention. Alternatively, the labeling agent may be a third moiety, such as another antibody, that specifically binds to the antibody/protein complex.

In a preferred embodiment, the labeling agent is a second antibody bearing a label. Alternatively, the second antibody may lack a label, but it may, in turn, be bound 10 by a labeled third antibody specific to antibodies of the species from which the second antibody is derived. The second can be modified with a detectable moiety, such as biotin, to which a third labeled molecule can specifically bind, such as enzyme-labeled streptavidin.

Other proteins capable of specifically binding immunoglobulin constant regions, 15 such as protein A or protein G may also be used as the label agent. These proteins are normal constituents of the cell walls of streptococcal bacteria. They exhibit a strong non-immunogenic reactivity with immunoglobulin constant regions from a variety of species (See, generally Kronval, *et al.*, *J. Immunol.* 111: 1401-1406 (1973), and Akerstrom, *et al.*, *J. Immunol.* 135: 2589-2542 (1985)).

20 Throughout the assays, incubation and/or washing steps may be required after each combination of reagents. Incubation steps can vary from about 5 seconds to several hours, preferably from about 5 minutes to about 24 hours. However, the incubation time will depend upon the assay format, analyte, volume of solution, concentrations, and the like. Usually, the assays will be carried out at ambient temperature, although they can 25 be conducted over a range of temperatures, such as 10°C to 40°C.

While the details of the immunoassays of the present invention may vary with the particular format employed, the method of detecting a protein of the present invention in a biological sample generally comprises the steps of contacting the biological sample with an antibody which specifically reacts, under immunologically reactive conditions, to 30 a protein of the present invention. The antibody is allowed to bind to the protein under immunologically reactive conditions, and the presence of the bound antibody is detected directly or indirectly.

A. Non-Competitive Assay Formats

Immunoassays for detecting proteins of the present invention include competitive and noncompetitive formats. Noncompetitive immunoassays are assays in which the amount of captured analyte (i.e., a protein of the present invention) is directly measured. In one preferred "sandwich" assay, for example, the capture agent (e.g., an antibody specifically reactive, under immunoreactive conditions, to a protein of the present invention) can be bound directly to a solid substrate where they are immobilized. These immobilized antibodies then capture the protein present in the test sample. The protein thus immobilized is then bound by a labeling agent, such as a second antibody bearing a label. Alternatively, the second antibody may lack a label, but it may, in turn, be bound by a labeled third antibody specific to antibodies of the species from which the second antibody is derived. The second can be modified with a detectable moiety, such as biotin, to which a third labeled molecule can specifically bind, such as enzyme-labeled streptavidin.

15

B. Competitive Assay Formats

In competitive assays, the amount of analyte present in the sample is measured indirectly by measuring the amount of an added (exogenous) analyte (e.g., a protein of the present invention) displaced (or competed away) from a capture agent (e.g., an antibody specifically reactive, under immunoreactive conditions, to the protein) by the analyte present in the sample. In one competitive assay, a known amount of analyte is added to the sample and the sample is then contacted with a capture agent that specifically binds a protein of the present invention. The amount of protein bound to the capture agent is inversely proportional to the concentration of analyte present in the sample.

25 In a particularly preferred embodiment, the antibody is immobilized on a solid substrate. The amount of protein bound to the antibody may be determined either by measuring the amount of protein present in a protein/antibody complex, or alternatively by measuring the amount of remaining uncomplexed protein. The amount of protein may 30 be detected by providing a labeled protein.

A hapten inhibition assay is another preferred competitive assay. In this assay a known analyte, (such as a protein of the present invention) is immobilized on a solid substrate. A known amount of antibody specifically reactive, under immunoreactive

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conditions, to the protein is added to the sample, and the sample is then contacted with the immobilized protein. In this case, the amount of antibody bound to the immobilized protein is inversely proportional to the amount of protein present in the sample. Again, the amount of immobilized antibody may be detected by detecting either the immobilized fraction of antibody or the fraction of the antibody that remains in solution. Detection may be direct where the antibody is labeled or indirect by the subsequent addition of a labeled moiety that specifically binds to the antibody as described above.

C. Generation of pooled antisera for use in immunoassays

10 A protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen is determined in an immunoassay. The immunoassay uses a polyclonal antiserum which is raised to a polypeptide of the present invention (i.e., the immunogenic polypeptide). This antiserum is selected to have low crossreactivity against other proteins and any such crossreactivity is removed by
15 immunoabsorption prior to use in the immunoassay (e.g., by immunosorption of the antisera with a protein of different substrate specificity (e.g., a different enzyme) and/or a protein with the same substrate specificity but of a different form).

In order to produce antisera for use in an immunoassay, a polypeptide of the present invention is isolated as described herein. For example, recombinant protein can
20 be produced in a mammalian or other eukaryotic cell line. An inbred strain of mice is immunized with the protein using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, above). Alternatively, a synthetic polypeptide derived from the sequences disclosed herein and conjugated to a carrier protein is used as an immunogen. Polyclonal sera are collected and titered
25 against the immunogenic polypeptide in an immunoassay, for example, a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against polypeptides of different forms or substrate specificity, using a competitive binding immunoassay such as the one described in Harlow and Lane, above, at pages 570-573.
30 Preferably, two or more distinct forms of polypeptides are used in this determination. These distinct types of polypeptides are used as competitors to identify antibodies which are specifically bound by the polypeptide being assayed for. The competitive

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polypeptides can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

Immunoassays in the competitive binding format are used for crossreactivity determinations. For example, the immunogenic polypeptide is immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the immunogenic polypeptide. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with a distinct form of a polypeptide are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with a distinct form of a polypeptide.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described herein to compare a second "target" polypeptide to the immunogenic polypeptide. In order to make this comparison, the two polypeptides are each assayed at a wide range of concentrations and the amount of each polypeptide required to inhibit 50% of the binding of the antisera to the immobilized protein is determined using standard techniques. If the amount of the target polypeptide required is less than twice the amount of the immunogenic polypeptide that is required, then the target polypeptide is said to specifically bind to an antibody generated to the immunogenic protein. As a final determination of specificity, the pooled antisera is fully immunosorbed with the immunogenic polypeptide until no binding to the polypeptide used in the immunosorption is detectable. The fully immunosorbed antisera is then tested for reactivity with the test polypeptide. If no reactivity is observed, then the test polypeptide is specifically bound by the antisera elicited by the immunogenic protein.

25

D. Other Assay Formats

In a particularly preferred embodiment, Western blot (immunoblot) analysis is used to detect and quantify the presence of protein of the present invention in the sample. The technique generally comprises separating sample proteins by gel electrophoresis on the basis of molecular weight, transferring the separated proteins to a suitable solid support, (such as a nitrocellulose filter, a nylon filter, or derivatized nylon filter), and incubating the sample with the antibodies that specifically bind a protein of the present invention. The antibodies specifically bind to the protein on the solid support. These

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antibodies may be directly labeled or alternatively may be subsequently detected using labeled antibodies (*e.g.*, labeled sheep anti-mouse antibodies) that specifically bind to the antibodies.

5

E. Quantification of Proteins.

The proteins of the present invention may be detected and quantified by any of a number of means well known to those of skill in the art. These include analytic biochemical methods such as electrophoresis, capillary electrophoresis, high performance
10 liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, and the like, and various immunological methods such as fluid or gel precipitin reactions, immunodiffusion (single or double), immunolectrophoresis, radioimmunoassays (RIAs), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, and the like.

15

F. Reduction of Non-Specific Binding

One of skill will appreciate that it is often desirable to reduce non-specific binding in immunoassays and during analyte purification. Where the assay involves an antigen, antibody, or other capture agent immobilized on a solid substrate, it is desirable
20 to minimize the amount of non-specific binding to the substrate. Means of reducing such non-specific binding are well known to those of skill in the art. Typically, this involves coating the substrate with a proteinaceous composition. In particular, protein compositions such as bovine serum albumin (BSA), nonfat powdered milk, and gelatin are widely used.

25

G. Immunoassay Labels

The labeling agent can be, *e.g.*, a monoclonal antibody, a polyclonal antibody, a binding protein or complex, or a polymer such as an affinity matrix, carbohydrate or lipid. Detectable labels suitable for use in the present invention include any composition
30 detectable by spectroscopic, radioisotopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Detection may proceed by any known method, such as immunoblotting, western analysis, gel-mobility shift assays, fluorescent *in situ* hybridization analysis (FISH), tracking of radioactive or

- bioluminescent markers, nuclear magnetic resonance, electron paramagnetic resonance, stopped-flow spectroscopy, column chromatography, capillary electrophoresis, or other methods which track a molecule based upon an alteration in size and/or charge. The particular label or detectable group used in the assay is not a critical aspect of the invention. The detectable group can be any material having a detectable physical or chemical property. Such detectable labels have been well-developed in the field of immunoassays and, in general, any label useful in such methods can be applied to the present invention. Thus, a label is any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means.
- 10 Useful labels in the present invention include magnetic beads, fluorescent dyes, radiolabels, enzymes, and colorimetric labels or colored glass or plastic beads, as discussed for nucleic acid labels, above.
- The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. As indicated above, a wide variety of labels may be used, with the choice of label depending on the sensitivity required, ease of conjugation of the compound, stability requirements, available instrumentation, and disposal provisions.
- 15 Non-radioactive labels are often attached by indirect means. Generally, a ligand molecule (*e.g.*, biotin) is covalently bound to the molecule. The ligand then binds to an anti-ligand (*e.g.*, streptavidin) molecule which is either inherently detectable or covalently bound to a signal system, such as a detectable enzyme, a fluorescent compound, or a chemiluminescent compound. A number of ligands and anti-ligands can be used. Where a ligand has a natural anti-ligand, for example, biotin, thyroxine, and cortisol, it can be used in conjunction with the labeled, naturally occurring anti-ligands.
- 20 Alternatively, any haptenic or antigenic compound can be used in combination with an antibody.

The molecules can also be conjugated directly to signal generating compounds, *e.g.*, by conjugation with an enzyme or fluorophore. Enzymes of interest as labels will primarily be hydrolases, particularly phosphatases, esterases and glycosidases, or 30 oxidoreductases, particularly peroxidases. Fluorescent compounds include fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, etc. Chemiluminescent compounds include luciferin, and 2,3-dihydropthalazinediones, *e.g.*,

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luminol. For a review of various labeling or signal producing systems which may be used, see, U.S. Patent No. 4,391,904, which is incorporated herein by reference.

Means of detecting labels are well known to those of skill in the art. Thus, for example, where the label is a radioactive label, means for detection include a scintillation counter or photographic film as in autoradiography. Where the label is a fluorescent label, it may be detected by exciting the fluorochrome with the appropriate wavelength of light and detecting the resulting fluorescence, *e.g.*, by microscopy, visual inspection, via photographic film, by the use of electronic detectors such as charge coupled devices (CCDs) or photomultipliers and the like. Similarly, enzymatic labels may be detected by providing appropriate substrates for the enzyme and detecting the resulting reaction product. Finally, simple colorimetric labels may be detected simply by observing the color associated with the label. Thus, in various dipstick assays, conjugated gold often appears pink, while various conjugated beads appear the color of the bead.

Some assay formats do not require the use of labeled components. For instance, agglutination assays can be used to detect the presence of the target antibodies. In this case, antigen-coated particles are agglutinated by samples comprising the target antibodies. In this format, none of the components need be labeled and the presence of the target antibody is detected by simple visual inspection.

20 **Assays for Compounds that Modulate Enzymatic Activity or Expression**

The present invention also provides means for identifying compounds that bind to (e.g., substrates), and/or increase or decrease (i.e., modulate) the enzymatic activity of, catalytically active polypeptides of the present invention. The method comprises contacting a polypeptide of the present invention with a compound whose ability to bind to or modulate enzyme activity is to be determined. The polypeptide employed will have at least 20%, preferably at least 30% or 40%, more preferably at least 50% or 60%, and most preferably at least 70% or 80% of the specific activity of the native, full-length polypeptide of the present invention (e.g., enzyme). Generally, the polypeptide will be present in a range sufficient to determine the effect of the compound, typically about 1 nM to 10 μ M. Likewise, the compound will be present in a concentration of from about 1 nM to 10 μ M. Those of skill will understand that such factors as enzyme concentration, ligand concentrations (i.e., substrates, products, inhibitors, activators), pH, ionic strength, and temperature will be controlled so as to obtain useful kinetic data

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and determine the presence or absence of a compound that binds or modulates polypeptide activity. Methods of measuring enzyme kinetics is well known in the art. See, e.g., Segel, *Biochemical Calculations*, 2nd ed., John Wiley and Sons, New York (1976).

5 Although the present invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

10 **Example 1**

This example describes the construction cDNA libraries.

Total RNA Isolation

15 Total RNA was isolated from corn tissues with TRIzol Reagent (Life Technology Inc. Gaithersburg, MD) using a modification of the guanidine isothiocyanate/acid-phenol procedure described by Chomczynski and Sacchi (Chomczynski, P., and Sacchi, N. *Anal. Biochem.* 162, 156 (1987)). In brief, plant tissue samples were pulverized in liquid nitrogen before the addition of the TRIzol Reagent, and then were further homogenized with a mortar and pestle. Addition of chloroform followed by
20 centrifugation was conducted for separation of an aqueous phase and an organic phase. The total RNA was recovered by precipitation with isopropyl alcohol from the aqueous phase.

Poly(A)+ RNA Isolation

25 The selection of poly(A)+ RNA from total RNA was performed using PolyATact system (Promega Corporation. Madison, WI). In brief, biotinylated oligo(dT) primers were used to hybridize to the 3' poly(A) tails on mRNA. The hybrids were captured using streptavidin coupled to paramagnetic particles and a magnetic separation stand. The mRNA was washed at high stringent condition and eluted by RNase-free deionized
30 water.

cDNA Library Construction

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- cDNA synthesis was performed and unidirectional cDNA libraries were constructed using the SuperScript Plasmid System (Life Technology Inc. Gaithersburg, MD). The first stand of cDNA was synthesized by priming an oligo(dT) primer containing a Not I site. The reaction was catalyzed by SuperScript Reverse Transcriptase II at 45°C. The second strand of cDNA was labeled with alpha-³²P-dCTP and a portion of the reaction was analyzed by agarose gel electrophoresis to determine cDNA sizes. cDNA molecules smaller than 500 base pairs and unligated adapters were removed by Sephadex-S400 chromatography. The selected cDNA molecules were ligated into pSPORT1 vector in between of Not I and Sal I sites.

10

Example 2

This example describes cDNA sequencing and library subtraction.

Sequencing Template Preparation

- Individual colonies were picked and DNA was prepared either by PCR with M13 forward primers and M13 reverse primers, or by plasmid isolation. All the cDNA clones were sequenced using M13 reverse primers.

Q-bot Subtraction Procedure

- cDNA libraries subjected to the subtraction procedure were plated out on 22 x 22 cm² agar plate at density of about 3,000 colonies per plate. The plates were incubated in a 37°C incubator for 12-24 hours. Colonies were picked into 384-well plates by a robot colony picker, Q-bot (GENETIX Limited). These plates were incubated overnight at 37°C.

- Once sufficient colonies were picked, they were pinned onto 22 x 22 cm² nylon membranes using Q-bot. Each membrane contained 9,216 colonies or 36,864 colonies. These membranes were placed onto agar plate with appropriate antibiotic. The plates were incubated at 37°C for overnight.

- After colonies were recovered on the second day, these filters were placed on filter paper prewetted with denaturing solution for four minutes, then were incubated on top of a boiling water bath for additional four minutes. The filters were then placed on filter paper prewetted with neutralizing solution for four minutes. After excess solution was removed by placing the filters on dry filter papers for one minute, the colony side of the filters were place into Proteinase K solution, incubated at 37°C for 40-50 minutes.

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The filters were placed on dry filter papers to dry overnight. DNA was then cross-linked to nylon membrane by UV light treatment.

Colony hybridization was conducted as described by Sambrook, J., Fritsch, E.F. and Maniatis, T., (in Molecular Cloning: A laboratory Manual, 2nd Edition). The 5 following probes were used in colony hybridization:

1. First strand cDNA from the same tissue as the library was made from to remove the most redundant clones.
2. 48-192 most redundant cDNA clones from the same library based on previous sequencing data.
- 10 3. 192 most redundant cDNA clones in the entire corn partial sequence database.
4. A Sal-A20 oligo nucleotide: TCG ACC CAC GCG TCC GAA AAA AAA AAA AAA AAA AAA AAA, removes clones containing a poly A tail but no cDNA.
5. cDNA clones derived from rRNA.

The image of the autoradiography was scanned into computer and the signal intensity and 15 cold colony addresses of each colony was analyzed. Re-arraying of cold-colonies from 384 well plates to 96 well plates was conducted using Q-bot.

Example 3

This example describes identification of the gene from a computer homology 20 search. Gene identities were determined by conducting BLAST (Basic Local Alignment Search Tool; Altschul, S. F., et al., (1993) *J. Mol. Biol.* 215:403-410; see also www.ncbi.nlm.nih.gov/BLAST/) searches under default parameters for similarity to sequences contained in the BLAST "nr" database (comprising all non-redundant GenBank CDS translations, sequences derived from the 3-dimensional structure 25 Brookhaven Protein Data Bank, the last major release of the SWISS-PROT protein sequence database, EMBL, and DDBJ databases). The cDNA sequences were analyzed for similarity to all publicly available DNA sequences contained in the "nr" database using the BLASTN algorithm. The DNA sequences were translated in all reading frames and compared for similarity to all publicly available protein sequences contained in the 30 "nr" database using the BLASTX algorithm (Gish, W. and States, D. J. (1993) *Nature Genetics* 3:266-272) provided by the NCBI. In some cases, the sequencing data from two or more clones containing overlapping segments of DNA were used to construct contiguous DNA sequences.

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The above examples are provided to illustrate the invention but not to limit its scope. Other variants of the invention will be readily apparent to one of ordinary skill in the art and are encompassed by the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid comprising a member selected from the group consisting of:
 - 5 (a) a polynucleotide having at least 80% sequence identity, as determined by the BLAST 2.0 algorithm under default parameters, to a polynucleotide encoding a polypeptide selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58
 - 10 (b) a polynucleotide encoding a polypeptide of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58
 - (c) a polynucleotide amplified from a *Zea mays* nucleic acid library using primers which selectively hybridize, under stringent hybridization conditions, to loci within a polynucleotide selected from the group consisting of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57
 - 15 (d) a polynucleotide which selectively hybridizes, under stringent hybridization conditions and a wash in 2X SSC at 50°C, to a polynucleotide of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57
 - (e) a polynucleotide of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57
 - 20 (f) a polynucleotide which is complementary to a polynucleotide of (a), (b), (c), (d), or (e); and
 - (g) a polynucleotide comprising at least 25 contiguous nucleotides from a polynucleotide of (a), (b), (c), (d), (e), or (f).
- 25 2. A recombinant expression cassette, comprising a member of claim 1 operably linked, in sense or anti-sense orientation, to a promoter.
3. A host cell comprising the recombinant expression cassette of claim 2.
- 30 4. A transgenic plant comprising a recombinant expression cassette of claim 2.
5. The transgenic plant of claim 4, wherein the plant is a monocot.

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6. The transgenic plant of claim 4, wherein the plant is selected from the group consisting of: maize, soybean, sunflower, sorghum, canola, wheat, alfalfa, cotton, rice, barley, and millet.
- 5 7. A transgenic seed from the transgenic plant of claim 4.
8. A method of modulating the level of cellulose synthase in a plant cell capable of plant regeneration, comprising:
 - (a) transforming the plant cell with a recombinant expression cassette comprising a cellulose synthase polynucleotide of claim 1 operably linked to a promoter;
 - 10 (b) culturing the transformed plant cell; and
 - (c) inducing expression of said polynucleotide for a time sufficient to modulate the level of cellulose synthase in said transformed plant cell.
- 15 9. The method of claim 8, wherein a plant is regenerated from the transformed plant cell.
10. The method of claim 9, wherein the plant is selected from the group consisting of : maize, soybean, sunflower, sorghum, canola, wheat, alfalfa, cotton, rice, barley, and millet.
- 20 11. The method of claim 8, wherein the promoter is a tissue-preferred promoter.
12. The method of claim 8, wherein the level of cellulose synthase is increased.
- 25 13. The method of claim 8 wherein the cell cycle polynucleotide is amplified from a *Zea mays* nucleic acid library using primers which selectively hybridize, under stringent hybridization conditions, to loci within a polynucleotide selected from the group consisting of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57.
- 30 14. The method of claim 8 wherein the cell cycle gene is selected from the group consisting of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57.

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15. An isolated protein comprising a member selected from the group consisting of:
 - (a) a polypeptide of at least 20 contiguous amino acids from a polypeptide of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58
 - (b) a polypeptide of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46,
5 50, 54, and 58
 - (c) a polypeptide having at least 80% sequence identity to, and having at least one linear epitope in common with, a polypeptide of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58, wherein said sequence identity is determined using BLAST 2.0 under default parameters; and,
 - 10 (d) a polypeptide encoded by a member of claim 1.

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SEQUENCE LISTING

<110> Pioneer Hi-Bred International, Inc.

<120> Maize Cellulose Synthases and Uses
Thereof

<130> 0864-PCT

<150> 60/096,822

<151> August 17, 1998

<160> 60

<170> FastSEQ for Windows Version 3.0

<210> 1

<211> 3568

<212> DNA

<213> Zea mays

<220>

<221> CDS

<222> (63)...(3237)

<400> 1

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cc atg	gac	cag	cgg	aac	ggc	107
Met	Asp	Gln	Arg	Asn	Gly	
1	5	10	15			

gtg	ggg	cgc	aac	ccc	gac	ggg	gag	cct	ttc	gtg	gcc	tgc	aac	gag	tgc	155
Val	Gly	Arg	Asn	Pro	Asp	Gly	Pro	Phe	Val	Ala	Cys	Asn	Glu	Cys		
20	25	30														

gcc	ttc	ccc	atc	tgc	cgg	gac	tgc	tac	gag	tac	gag	cgc	cgc	gag	ggc	203
Ala	Phe	Pro	Ile	Cys	Arg	Asp	Cys	Tyr	Glu	Tyr	Glu	Arg	Arg	Glu	Gly	
35	40	45														

acg	cag	aac	tgc	ccc	cag	tgc	aag	acc	cgc	ttc	aag	cgc	ttc	aag	ggg	251
Thr	Gln	Asn	Cys	Pro	Gln	Cys	Lys	Thr	Arg	Phe	Lys	Arg	Phe	Lys	Gly	
50	55	60														

tgc	gcf	cgc	gtg	ccc	ggg	gac	gag	gag	gac	ggc	gtc	gac	gac	ctg	299
Cys	Ala	Arg	Val	Pro	Gly	Asp	Glu	Glu	Asp	Gly	Val	Asp	Asp	Leu	
65	70	75													

gag	aac	gag	ttc	aac	tgg	agc	aag	cac	gac	tcc	cag	tac	ctc	gcc	347
Glu	Asn	Glu	Phe	Asn	Trp	Ser	Asp	Lys	His	Asp	Ser	Gln	Tyr	Leu	Ala
80	85	90													

gag	tcc	atg	ctc	cac	gcc	cac	atg	agc	tac	ggc	cgc	ggc	gcc	gac	395
Glu	Ser	Met	Leu	His	Ala	His	Met	Ser	Tyr	Gly	Arg	Gly	Ala	Asp	Leu
100	105	110													

gac	ggc	gtg	ccg	cag	cca	ttc	cac	ccc	atc	ccc	aat	gtt	ccc	ctc	ctc	443
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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Asp Gly Val Pro Gln Pro Phe His Pro Ile Pro Asn Val Pro Leu Leu		
115	120	125
acc aac gga cag atg gtc gat gac atc ccg ccg gac cag cac gcc ctt		
Thr Asn Gly Gln Met Val Asp Asp Ile Pro Pro Asp Gln His Ala Leu		
130	135	140
491		
gtg ccc tcg ttc gtg ggt ggc ggg ggg aag agg att cac cct ctc ccg		
Val Pro Ser Phe Val Gly Gly Gly Lys Arg Ile His Pro Leu Pro		
145	150	155
539		
tac gcg gat ccc aac ctt cct gtg caa ccg agg tct atg gac cct tcc		
Tyr Ala Asp Pro Asn Leu Pro Val Gln Pro Arg Ser Met Asp Pro Ser		
160	165	170
587		
aag gat ctc gcc gca tat ggc tac ggg agc gta gca tgg aag gag agg		
Lys Asp Leu Ala Ala Tyr Gly Tyr Gly Ser Val Ala Trp Lys Glu Arg		
180	185	190
635		
atg gag agc tgg aag cag aag cag gag agg atg cac cag acg agg aac		
Met Glu Ser Trp Lys Gln Lys Glu Arg Met His Gln Thr Arg Asn		
195	200	205
683		
gat ggc ggc ggc gat gat ggt gat gat gca gat cta cca cta atg gat		
Asp Gly Gly Asp Asp Gly Asp Asp Ala Asp Leu Pro Leu Met Asp		
210	215	220
731		
gaa gct aga cag cca ttg tcc aga aag atc ccg ctt cct tca agc caa		
Glu Ala Arg Gln Pro Leu Ser Arg Lys Ile Pro Leu Pro Ser Ser Gln		
225	230	235
779		
atc aac ccc tat agg atg att ata ata att cgg cta gtg gtt ttg tgt		
Ile Asn Pro Tyr Arg Met Ile Ile Ile Ile Arg Leu Val Val Leu Cys		
240	245	250
255		
827		
ttc ttc ttc cac tac cga gtg atg cat ccg gtg cct gat gca ttt gct		
Phe Phe Phe His Tyr Arg Val Met His Pro Val Pro Asp Ala Phe Ala		
260	265	270
875		
tta tgg ctc ata tct gtg atc tgt gaa att tgg ttt gcc atg tct tgg		
Leu Trp Leu Ile Ser Val Ile Cys Glu Ile Trp Phe Ala Met Ser Trp		
275	280	285
923		
att ctt gac cag ttt cca aag tgg ttt cct atc gag agg gaa acc tat		
Ile Leu Asp Gln Phe Pro Lys Trp Phe Pro Ile Glu Arg Glu Thr Tyr		
290	295	300
971		
ctt gac cgg ctg agt tta agg ttt gac aag gaa ggg cat cct tct caa		
Leu Asp Arg Leu Ser Leu Arg Phe Asp Lys Glu Gly His Pro Ser Gln		
305	310	315
1019		
ctc gcc cct gtt gat ttc ttt gtc agt acg gtt gat ccc ttg aag gaa		
Leu Ala Pro Val Asp Phe Phe Val Ser Thr Val Asp Pro Leu Lys Glu		
320	325	330
335		
1067		
cct cca ttg gtc act gct aat act gtt cta tct atc ctt tcg gtg gat		
Pro Pro Leu Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ser Val Asp		
340	345	350
1115		

- 3 -

tat cca gtt gat aag gtt tca tgc tac gtt tct gat gat ggt gct gcc Tyr Pro Val Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ala Ala 355 360 365	1163
atg ctg aca ttt gaa gca ttg tct gaa aca tct gaa ttt gca aag aaa Met Leu Thr Phe Glu Ala Leu Ser Glu Thr Ser Glu Phe Ala Lys Lys 370 375 380	1211
tgg gtt cct ttc tgc aaa aga tat agc ctt gag cct cgt gct cca gag Trp Val Pro Phe Cys Lys Arg Tyr Ser Leu Glu Pro Arg Ala Pro Glu 385 390 395	1259
tgg tac ttc caa cag aag ata gac tac ctg aaa gac aag gtg gcg cca Trp Tyr Phe Gln Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val Ala Pro 400 405 410 415	1307
aac ttt gtt aga gaa cgg aga gca atg aag aga gag tat gag gaa ttc Asn Phe Val Arg Glu Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe 420 425 430	1355
aag gtc aga atc aat gcc ttg gtt gct aaa gcc caa aag gtt cct gag Lys Val Arg Ile Asn Ala Leu Val Ala Lys Ala Gln Lys Val Pro Glu 435 440 445	1403
gaa gga tgg aca atg cag gat gga act cca tgg ccc gga aat aat gtc Glu Gly Trp Thr Met Gln Asp Gly Thr Pro Trp Pro Gly Asn Asn Val 450 455 460	1451
cgt gat cat cct gga atg att cag gtt ttc ctt ggt caa agt ggt ggc Arg Asp His Pro Gly Met Ile Gln Val Phe Leu Gly Gln Ser Gly Gly 465 470 475	1499
cat gat gtg gaa gga aat gag ctg cct cga ttg gtt tat gtt tca aga His Asp Val Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg 480 485 490 495	1547
gaa aaa cgg cca ggc tac aac cat cac aag aag gct ggt gct atg aat Glu Lys Arg Pro Gly Tyr Asn His His Lys Lys Ala Gly Ala Met Asn 500 505 510	1595
gca ttg gtc cga gtc tct gct gta cta act aat gct cct tat ttg ctg Ala Leu Val Arg Val Ser Ala Val Leu Thr Asn Ala Pro Tyr Leu Leu 515 520 525	1643
aac ttg gat tgt gat cac tat atc aat aat agt aag gct ata aag gaa Asn Leu Asp Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Ile Lys Glu 530 535 540	1691
gca atg tgt ttt atg atg gat cct ttg ctt gga aag aaa gtt tgc tat Ala Met Cys Phe Met Met Asp Pro Leu Leu Gly Lys Lys Val Cys Tyr 545 550 555	1739
gtg cag ttt cct caa aga ttt gat ggg att gat cgc cat gat cga tat Val Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Arg His Asp Arg Tyr 560 565 570 575	1787
gct aac aga aat gtt gtc ttt ttc gat atc aac atg aaa ggt ttg gat	1835

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Ala Asn Arg Asn Val Val Phe Phe Asp Ile Asn Met Lys Gly Leu Asp	580	585	590
ggc cag ggc cca att tat gtg ggt act gga tgt gtc ttc aga agg			
Gly Ile Gln Gly Pro Ile Tyr Val Gly Thr Gly Cys Val Phe Arg Arg	595	600	605
cag gca tta tat ggc tac gat gct ccc aaa aca aag aag cca cca tca			
Gln Ala Leu Tyr Gly Tyr Asp Ala Pro Lys Thr Lys Lys Pro Pro Ser	610	615	620
aga act tgc aac tgc tgg cca aag tgg tgc att tgc tgt tgc tgt ttt			
Arg Thr Cys Asn Cys Trp Pro Lys Trp Cys Ile Cys Cys Cys Cys Phe	625	630	635
ggc aac agg aag acc aag aag aag acc aag acc tct aaa cct aaa ttt			
Gly Asn Arg Lys Thr Lys Lys Thr Lys Thr Ser Lys Pro Lys Phe	640	645	650
gag aag ata aag aaa ctt ttt aag aaa aag gaa aat caa gcc cct gca			
Glu Lys Ile Lys Lys Leu Phe Lys Lys Glu Asn Gln Ala Pro Ala	660	665	670
tat gct ctt ggt gaa att gat gaa gcc gct cca gga gct gaa aat gaa			
Tyr Ala Leu Gly Glu Ile Asp Glu Ala Ala Pro Gly Ala Glu Asn Glu	675	680	685
aag gct agt att gta aat caa cag aag ttg gaa aag aaa ttt ggc cag			
Lys Ala Ser Ile Val Asn Gln Gln Lys Leu Glu Lys Lys Phe Gly Gln	690	695	700
tct tca gtt ttt gtt gca tcc aca ctt ctt gag aat ggt gga acc ctg			
Ser Ser Val Phe Val Ala Ser Thr Leu Leu Glu Asn Gly Gly Thr Leu	705	710	715
aag agt gcc agt cca gct tct ctt ctg aag gaa gct ata cat gtc atc			
Lys Ser Ala Ser Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile	720	725	730
agt tgt gga tat gaa gac aaa aca ggc tgg gga aaa gat att ggt tgg			
Ser Cys Gly Tyr Glu Asp Lys Thr Gly Trp Gly Lys Asp Ile Gly Trp	740	745	750
att tat gga tca gtc aca gaa gat att ctt act ggg ttt aag atg cac			
Ile Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His	755	760	765
gc cat ggt tgg cgg tca att tac tgc ata cct aaa cgg gcc gcc ttc			
Lys His Gly Trp Arg Ser Ile Tyr Cys Ile Pro Lys Arg Ala Ala Phe	770	775	780
aa ggt tcc gca cct ctc aat ctt tcc gat cgt ttt cac cag gtt ctt			
Lys Gly Ser Ala Pro Leu Asn Leu Ser Asp Arg Phe His Gln Val Leu	785	790	795
gg tgg gct ctt ggt tca att gaa att ttg ttc agc aac cac tgc cct			
Arg Trp Ala Leu Gly Ser Ile Glu Ile Leu Phe Ser Asn His Cys Pro	800	805	810
			815

- 5 -

ctc tgg tat ggg tat ggt ggt gga cta aag ttc ctg gaa agg ttt tcg Leu Trp Tyr Gly Tyr Gly Gly Leu Lys Phe Leu Glu Arg Phe Ser 820 825 830	2555
tac att aac tcc atc gta tac cct tgg aca tct atc ccg ctc ttg gcc Tyr Ile Asn Ser Ile Val Tyr Pro Trp Thr Ser Ile Pro Leu Leu Ala 835 840 845	2603
tat tgc aca ttg cct gcc atc tgc ttg ctg aca ggg aaa ttt atc acg Tyr Cys Thr Leu Pro Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile Thr 850 855 860	2651
cca gag ctt aac aat gtt gcc agc ctc tgg ttc atg tca ctt ttc atc Pro Glu Leu Asn Asn Val Ala Ser Leu Trp Phe Met Ser Leu Phe Ile 865 870 875	2699
tgc att ttt gct acg agc atc ctg gaa atg aga tgg agt ggt gta ggc Cys Ile Phe Ala Thr Ser Ile Leu Glu Met Arg Trp Ser Gly Val Gly 880 885 890 895	2747
atc gat gac tgg tgg aga aac gag cag ttt tgg gtc att gga ggc gtg Ile Asp Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Val 900 905 910	2795
tct tca cat ctc ttt gct gtg ttc cag gga ctc ctc aag gtc ata gct Ser Ser His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Ile Ala 915 920 925	2843
ggg gta gac acg agc ttc act gtg aca tcc aag ggc gga gac gac gag Gly Val Asp Thr Ser Phe Thr Val Thr Ser Lys Gly Gly Asp Asp Glu 930 935 940	2891
gag ttc tca gag ctg tac aca ttc aaa tgg acg acc ctt ctg ata cct Glu Phe Ser Glu Leu Tyr Thr Phe Lys Trp Thr Thr Leu Leu Ile Pro 945 950 955	2939
ccg aca acc ctg ctc cta ctg aac ttc att gga gtg gta gct ggc atc Pro Thr Thr Leu Leu Leu Asn Phe Ile Gly Val Val Ala Gly Ile 960 965 970 975	2987
tcc aat gcg atc aac aac gga tat gaa tca tgg ggc ccc ctg ttc ggg Ser Asn Ala Ile Asn Asn Gly Tyr Glu Ser Trp Gly Pro Leu Phe Gly 980 985 990	3035
aag ctc ttc ttt gca ttt tgg gtg atc gtc cat ctt tac ccg ttc ctc Lys Leu Phe Phe Ala Phe Trp Val Ile Val His Leu Tyr Pro Phe Leu 995 1000 1005	3083
aag ggt ctg gtt ggg agg cag aac agg acg cca acg att gtc att gtc Lys Gly Leu Val Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val 1010 1015 1020	3131
tgg tcc atc ctc ctg gct tcg atc ttc tcg ctg ctt tgg gtc cggtt Trp Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Arg Ile 1025 1030 1035	3179
gac ccg ttc ctt gcg aag gat gat ggt ccc ctg ttg gag gag tgt ggt	3227

- 6 -

Asp Pro Phe Leu Ala Lys Asp Asp Gly Pro Leu Leu Glu Glu Cys Gly
 1040 1045 1050 1055

ctg gat tgc a actaggaggt cagcacgtgg acttcccggt cagtgtgtgg 3277
 Leu Asp Cys

tcgaagaagt attttgcaat atgtttgtg cccatattc tttactcaat ttttgtccct 3337
 ctgttagattt aaacaagggg tgaaggggaa aaaaagttact ttgtatccatg 3397
 gtgggtgggg tgggtggcgg ctcagccctg tgagtcaat attgggcaaa ccggagggtt 3457
 cggcaacctt gtgcagttcg tccacgaatn tactagggat gatgcgcacc aatcaatcaa 3517
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 <213> Zea mays

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 Phe Pro Ile Cys Arg Asp Cys Tyr Glu Tyr Glu Arg Arg Glu Gly Thr
 35 40 45
 Gln Asn Cys Pro Gln Cys Lys Thr Arg Phe Lys Arg Phe Lys Gly Cys
 50 55 60
 Ala Arg Val Pro Gly Asp Glu Glu Asp Gly Val Asp Asp Leu Glu
 65 70 75 80
 Asn Glu Phe Asn Trp Ser Asp Lys His Asp Ser Gln Tyr Leu Ala Glu
 85 90 95
 Ser Met Leu His Ala His Met Ser Tyr Gly Arg Gly Ala Asp Leu Asp
 100 105 110
 Gly Val Pro Gln Pro Phe His Pro Ile Pro Asn Val Pro Leu Leu Thr
 115 120 125
 Asn Gly Gln Met Val Asp Asp Ile Pro Pro Asp Gln His Ala Leu Val
 130 135 140
 Pro Ser Phe Val Gly Gly Gly Lys Arg Ile His Pro Leu Pro Tyr
 145 150 155 160
 Ala Asp Pro Asn Leu Pro Val Gln Pro Arg Ser Met Asp Pro Ser Lys
 165 170 175
 Asp Leu Ala Ala Tyr Gly Tyr Gly Ser Val Ala Trp Lys Glu Arg Met
 180 185 190
 Glu Ser Trp Lys Gln Lys Gln Glu Arg Met His Gln Thr Arg Asn Asp
 195 200 205
 Gly Gly Asp Asp Gly Asp Asp Ala Asp Leu Pro Leu Met Asp Glu
 210 215 220
 Ala Arg Gln Pro Leu Ser Arg Lys Ile Pro Leu Pro Ser Ser Gln Ile
 225 230 235 240
 Asn Pro Tyr Arg Met Ile Ile Ile Ile Arg Leu Val Val Leu Cys Phe
 245 250 255
 Phe Phe His Tyr Arg Val Met His Pro Val Pro Asp Ala Phe Ala Leu
 260 265 270
 Trp Leu Ile Ser Val Ile Cys Glu Ile Trp Phe Ala Met Ser Trp Ile
 275 280 285
 Leu Asp Gln Phe Pro Lys Trp Phe Pro Ile Glu Arg Glu Thr Tyr Leu
 290 295 300
 Asp Arg Leu Ser Leu Arg Phe Asp Lys Glu Gly His Pro Ser Gln Leu

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305	310	315	320
Ala Pro Val Asp Phe Phe Val Ser Thr Val Asp Pro Leu Lys Glu Pro			
325	330	335	
Pro Leu Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr			
340	345	350	
Pro Val Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ala Ala Met			
355	360	365	
Leu Thr Phe Glu Ala Leu Ser Glu Thr Ser Glu Phe Ala Lys Lys Trp			
370	375	380	
Val Pro Phe Cys Lys Arg Tyr Ser Leu Glu Pro Arg Ala Pro Glu Trp			
385	390	395	400
Tyr Phe Gln Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val Ala Pro Asn			
405	410	415	
Phe Val Arg Glu Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys			
420	425	430	
Val Arg Ile Asn Ala Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu			
435	440	445	
Gly Trp Thr Met Gln Asp Gly Thr Pro Trp Pro Gly Asn Asn Val Arg			
450	455	460	
Asp His Pro Gly Met Ile Gln Val Phe Leu Gly Gln Ser Gly Gly His			
465	470	475	480
Asp Val Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu			
485	490	495	
Lys Arg Pro Gly Tyr Asn His His Lys Lys Ala Gly Ala Met Asn Ala			
500	505	510	
Leu Val Arg Val Ser Ala Val Leu Thr Asn Ala Pro Tyr Leu Leu Asn			
515	520	525	
Leu Asp Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Ile Lys Glu Ala			
530	535	540	
Met Cys Phe Met Met Asp Pro Leu Leu Gly Lys Lys Val Cys Tyr Val			
545	550	555	560
Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Arg His Asp Arg Tyr Ala			
565	570	575	
Asn Arg Asn Val Val Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly			
580	585	590	
Ile Gln Gly Pro Ile Tyr Val Gly Thr Gly Cys Val Phe Arg Arg Gln			
595	600	605	
Ala Leu Tyr Gly Tyr Asp Ala Pro Lys Thr Lys Lys Pro Pro Ser Arg			
610	615	620	
Thr Cys Asn Cys Trp Pro Lys Trp Cys Ile Cys Cys Cys Phe Gly			
625	630	635	640
Asn Arg Lys Thr Lys Lys Thr Lys Thr Ser Lys Pro Lys Phe Glu			
645	650	655	
Lys Ile Lys Leu Phe Lys Lys Glu Asn Gln Ala Pro Ala Tyr			
660	665	670	
Ala Leu Gly Glu Ile Asp Glu Ala Ala Pro Gly Ala Glu Asn Glu Lys			
675	680	685	
Ala Ser Ile Val Asn Gln Gln Lys Leu Glu Lys Lys Phe Gly Gln Ser			
690	695	700	
Ser Val Phe Val Ala Ser Thr Leu Leu Glu Asn Gly Gly Thr Leu Lys			
705	710	715	720
Ser Ala Ser Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser			
725	730	735	
Cys Gly Tyr Glu Asp Lys Thr Gly Trp Gly Lys Asp Ile Gly Trp Ile			
740	745	750	
Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Cys			
755	760	765	
His Gly Trp Arg Ser Ile Tyr Cys Ile Pro Lys Arg Ala Ala Phe Lys			

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770	775	780
Gly Ser Ala Pro Leu Asn Leu Ser Asp Arg Phe His Gln Val Leu Arg		
785	790	795
Trp Ala Leu Gly Ser Ile Glu Ile Leu Phe Ser Asn His Cys Pro Leu		800
805	810	815
Trp Tyr Gly Tyr Gly Gly Leu Lys Phe Leu Glu Arg Phe Ser Tyr		
820	825	830
Ile Asn Ser Ile Val Tyr Pro Trp Thr Ser Ile Pro Leu Leu Ala Tyr		
835	840	845
Cys Thr Leu Pro Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile Thr Pro		
850	855	860
Glu Leu Asn Asn Val Ala Ser Leu Trp Phe Met Ser Leu Phe Ile Cys		
865	870	875
Ile Phe Ala Thr Ser Ile Leu Glu Met Arg Trp Ser Gly Val Gly Ile		880
885	890	895
Asp Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Val Ser		
900	905	910
Ser His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Ile Ala Gly		
915	920	925
Val Asp Thr Ser Phe Thr Val Thr Ser Lys Gly Gly Asp Asp Glu Glu		
930	935	940
Phe Ser Glu Leu Tyr Thr Phe Lys Trp Thr Thr Leu Leu Ile Pro Pro		
945	950	955
Thr Thr Leu Leu Leu Asn Phe Ile Gly Val Val Ala Gly Ile Ser		960
965	970	975
Asn Ala Ile Asn Asn Gly Tyr Glu Ser Trp Gly Pro Leu Phe Gly Lys		
980	985	990
Leu Phe Phe Ala Phe Trp Val Ile Val His Leu Tyr Pro Phe Leu Lys		
995	1000	1005
Gly Leu Val Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp		
1010	1015	1020
Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Arg Ile Asp		
1025	1030	1035
Pro Phe Leu Ala Lys Asp Asp Gly Pro Leu Leu Glu Glu Cys Gly Leu		1040
1045	1050	1055
Asp Cys Asn		

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<213> Zea mays

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atggaccagc ggaacggcca ggtgt
25

<210> 4
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<400> 4
ctagttgcaa tccagaccac actcc
25

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<212> DNA
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catcggtgcg	gtgcctgtc	cttttctc	gtccctcctc	ccccctata	gttaagcccc	180
gccccgtac	tactactact	agcagcagca	gegetctcgc	agcgggagat	gcggtgttga	240
tccgtgcccc	gctcggatct	cgggacttgt	gcccggcttg	cccaggcccc	aggctccagg	300
ccagctccct	cgacgttct	cgacgttct	gttgcc	atg	gag	355
				Met	Glu	
				Gly	Asp	Ala Asp
				1	5	
ggc	gtg	aag	tcg	ggg	agg	403
Gly	Val	Lys	Ser	Gly	Arg	
						403
10	15	20				
ggc	gac	ggc	gtg	ggc	acc	451
Gly	Asp	Gly	Val	Gly	Thr	
						451
25	30	35				
gac	gtc	tgc	ggg	ttt	ccg	499
Asp	Val	Cys	Gly	Phe	Pro	
						499
40	45	50				
aag	gac	ggc	acg	cag	gcg	547
Lys	Asp	Gly	Thr	Gln	Ala	
						547
55	60	65				
cac	aag	ggg	agc	ccg	gct	595
His	Lys	Gly	Ser	Pro	Ile	
						595
75	80	85				
gcc	gat	agc	gac	ttc	aat	643
Ala	Asp	Ser	Asp	Phe	Asn	
						643
90	95	100				
cag	aag	att	gcc	gac	aga	691
Gln	Lys	Ile	Ala	Asp	Arg	
						691
105	110	115				
agc	ggg	gat	gtt	ggc	ccc	739
Ser	Gly	Asp	Val	Gly	Arg	
						739
120	125	130				
acc	aag	tat	gac	agt	ggc	787
Thr	Lys	Tyr	Asp	Ser	Gly	
						787
135	140	145				
act	aac	agc	cag	atc	tca	835
Thr	Asn	Ser	Gln	Ile	Ser	
						835
155	160	165				
cat	atg	atg	tcc	cca	act	883

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His Met Met Ser Pro Thr Gly Asn Ile Gly Lys Arg Ala Pro Phe Pro			
170	175	180	
tat gtg aac cat tcg cca aat ccg tca agg gag ttc tct ggt agc att			
Tyr Val Asn His Ser Pro Asn Pro Ser Arg Glu Phe Ser Gly Ser Ile			931
185	190	195	
ggg aat gtt gcc tgg aaa gag agg gtt gat ggc tgg aaa atg aag cag			
Gly Asn Val Ala Trp Lys Glu Arg Val Asp Gly Trp Lys Met Lys Gln			979
200	205	210	
gac aag ggg acg att ccc atg acg aat ggc aca agc att gct ccc tct			
Asp Lys Gly Thr Ile Pro Met Thr Asn Gly Thr Ser Ile Ala Pro Ser			1027
215	220	225	230
gag ggt cgg ggt gtt gat att gat gca tca act gat tac aac atg			
Glu Gly Arg Gly Val Gly Asp Ile Asp Ala Ser Thr Asp Tyr Asn Met			1075
235	240	245	
gaa gat gcc tta ttg aac gac gaa act cga cag cct cta tct agg aaa			
Glu Asp Ala Leu Leu Asn Asp Glu Thr Arg Gln Pro Leu Ser Arg Lys			1123
250	255	260	
gtt cca ctt cct tcc tcc agg ata aat cca tac agg atg gtc att gtg			
Val Pro Leu Pro Ser Ser Arg Ile Asn Pro Tyr Arg Met Val Ile Val			1171
265	270	275	
ctg cga ttg att gtt cta agc atc ttc ttg cac tac cgt atc aca aat			
Leu Arg Leu Ile Val Leu Ser Ile Phe Leu His Tyr Arg Ile Thr Asn			1219
280	285	290	
cct gtg cgc aat gca tac cca tta tgg ctt cta tct gtt ata tgt gag			
Pro Val Arg Asn Ala Tyr Pro Leu Trp Leu Leu Ser Val Ile Cys Glu			1267
295	300	305	310
atc tgg ttt gct ctt tcg tgg ata ttg gat cag ttc cct aag tgg ttt			
Ile Trp Phe Ala Leu Ser Trp Ile Leu Asp Gln Phe Pro Lys Trp Phe			1315
315	320	325	
cca atc aac cgg gag acg tac ctt gat agg ctg gca tta agg tat gac			
Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu Arg Tyr Asp			1363
330	335	340	
cgg gaa ggt gag cca tct cag ttg gct gct gtt gac att ttc gtc agt			
Arg Glu Gly Glu Pro Ser Gln Leu Ala Ala Val Asp Ile Phe Val Ser			1411
345	350	355	
aca gtc gac cca atg aag gag cct cct gtc act gcc aat acc gtg			
Thr Val Asp Pro Met Lys Glu Pro Pro Leu Val Thr Ala Asn Thr Val			1459
360	365	370	
cta tcc att ctt gct gtg gat tac cct gtg gat aag gtc tct tgc tat			
Leu Ser Ile Leu Ala Val Asp Tyr Pro Val Asp Lys Val Ser Cys Tyr			1507
375	380	385	390
gta tct gat gat gga gct gcg atg ctg aca ttt gat gca cta gct gag			
Val Ser Asp Asp Gly Ala Ala Met Leu Thr Phe Asp Ala Leu Ala Glu			1555
395	400	405	

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act tca gag ttt gct aga aaa tgg gta cca ttt gtt aag aag tac aac Thr Ser Glu Phe Ala Arg Lys Trp Val Pro Phe Val Lys Tyr Asn 410 415 420	1603
att gaa cct aga gct cct gaa tgg tac ttc tcc cag aaa att gat tac Ile Glu Pro Arg Ala Pro Glu Trp Tyr Phe Ser Gln Lys Ile Asp Tyr 425 430 435	1651
ttg aag gac aaa gtg cac cct tca ttt gtt aaa gac cgc cggtt gac Leu Lys Asp Lys Val His Pro Ser Phe Val Lys Asp Arg Arg Ala Met 440 445 450	1699
aag aga gaa tat gaa gaa ttc aaa gtt agg gta aat ggc ctt gtt gct Lys Arg Glu Tyr Glu Phe Lys Val Arg Val Asn Gly Leu Val Ala 455 460 465 470	1747
aag gca cag aaa gtt cct gag gaa gga tgg atc atg caa gat ggc aca Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Ile Met Gln Asp Gly Thr 475 480 485	1795
cca tgg cca gga aac aat acc mgg gac cat cct gga atg att cag gtt Pro Trp Pro Gly Asn Asn Thr Xaa Asp His Pro Gly Met Ile Gln Val 490 495 500	1843
ttc ctt ggt cac agt ggt ggc ctt gat act gag ggc aat gag cta ccc Phe Leu Gly His Ser Gly Leu Asp Thr Glu Gly Asn Glu Leu Pro 505 510 515	1891
cgt ttg gtc tat gtt tct cgt gaa aag cgt cct gga ttc cag cat cac Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe Gln His His 520 525 530	1939
aag aaa gct ggt gcc atg aat got ctt gtt cgt gtc tca gct gtg ctt Lys Lys Ala Gly Ala Met Asn Ala Leu Val Arg Val Ser Ala Val Leu 535 540 545 550	1987
acc aat gga caa tac atg ttg aat ctt gat tgt gat cac tac att aac Thr Asn Gly Gln Tyr Met Leu Asn Leu Asp Cys Asp His Tyr Ile Asn 555 560 565	2035
aac agt aag gct ctc agg gaa gct atg tgc ttc ctt atg gac cct aac Asn Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Leu Met Asp Pro Asn 570 575 580	2083
cta gga agg agt gtc tgc tac gtc cag ttt ccc cag aga ttc gat ggc Leu Gly Arg Ser Val Cys Tyr Val Gln Phe Pro Gln Arg Phe Asp Gly 585 590 595	2131
att gac agg aat gat cga tat gcc aac agg aac acc gtg ttt ttc gat Ile Asp Arg Asn Asp Arg Tyr Ala Asn Arg Asn Thr Val Phe Phe Asp 600 605 610	2179
att aac ttg aga ggt ctt gat ggc atc caa gga cca gtt tat gtc gga Ile Asn Leu Arg Gly Leu Asp Gly Ile Gln Gly Pro Val Tyr Val Gly 615 620 625 630	2227
act ggc tgt gtt ttc aac cga aca gct cta tat ggt tat gag ccc cca	2275

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Thr Gly Cys Val Phe Asn Arg Thr Ala Leu Tyr Gly Tyr Glu Pro Pro			
635	640	645	
att aag cag aag aag ggt ggt ttc ttg tca tca cta tgt ggc ggt agg		2323	
Ile Lys Gln Lys Lys Gly Gly Phe Leu Ser Ser Leu Cys Gly Gly Arg			
650	655	660	
aag aag gca agc aaa tca aag aag ggc tcg gac aag aag tcg cag		2371	
Lys Lys Ala Ser Lys Ser Lys Gly Ser Asp Lys Lys Ser Gln			
665	670	675	
aag cat gtg gac agt tct gtg cca gta ttc aac ctt gaa gat ata gag		2419	
Lys His Val Asp Ser Ser Val Pro Val Phe Asn Leu Glu Asp Ile Glu			
680	685	690	
gag gga gtt gaa ggc gct gga ttt gac gac gag aaa tca ctt ctt atg		2467	
Glu Gly Val Glu Gly Ala Gly Phe Asp Asp Glu Lys Ser Leu Leu Met			
695	700	710	
tct caa atg agc ctg gag aag aga ttt ggc cag tcc gca gcg ttt gtt		2515	
Ser Gln Met Ser Leu Glu Lys Arg Phe Gly Gln Ser Ala Ala Phe Val			
715	720	725	
gcc tcc act ctg atg gag tat ggt ggt gtt cct cag tcc gca act ccg		2563	
Ala Ser Thr Leu Met Glu Tyr Gly Val Pro Gln Ser Ala Thr Pro			
730	735	740	
gag tct ctt ctg aaa gaa gct atc cat gtt ata agc tgt ggc tat gag		2611	
Glu Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly Tyr Glu			
745	750	755	
gac aag act gaa tgg gga act gag atc ggg tgg atc tac ggt tct gtg		2659	
Asp Lys Thr Glu Trp Gly Thr Glu Ile Gly Trp Ile Tyr Gly Ser Val			
760	765	770	
aca gaa gac att ctc acc gga ttc aag atg cac gcg cga ggc tgg cgg		2707	
Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg Gly Trp Arg			
775	780	785	790
tcg atc tac tgc atg ccc aag cgg cca gct ttc aag ggg tct gcc ccc		2755	
Ser Ile Tyr Cys Met Pro Lys Arg Pro Ala Phe Lys Gly Ser Ala Pro			
795	800	805	
atc aat ctt tcg gac cgt ctg aac cag gtg ctc cgg tgg gct ctt ggg		2803	
Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp Ala Leu Gly			
810	815	820	
tcc gtg gag atc ctc ttc agc cgg cac tgc ccc ctg tgg tac ggc tac		2851	
Ser Val Glu Ile Leu Phe Ser Arg His Cys Pro Leu Trp Tyr Gly Tyr			
825	830	835	
gga ggg cgg ctc aag ttc ctg gag aga ttc gcg tac atc aac acc acc		2899	
Gly Gly Arg Leu Lys Phe Leu Glu Arg Phe Ala Tyr Ile Asn Thr Thr			
840	845	850	
atc tac ccg ctc acg tcc atc ccg ctt ctc atc tac tgc atc ctg ccc		2947	
Ile Tyr Pro Leu Thr Ser Ile Pro Leu Leu Ile Tyr Cys Ile Leu Pro			
855	860	865	870

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gcc atc tgt ctg ctc acc gga aag ttc atc att cca gag atc agc aac Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile Ile Pro Glu Ile Ser Asn 875 880 885	2995
ttc gcc agc atc tgg ttc atc tcc ctc ttc atc tcg atc ttc gcc acg Phe Ala Ser Ile Trp Phe Ile Ser Leu Phe Ile Ser Ile Phe Ala Thr 890 895 900	3043
ggc atc ctg gag atg agg tgg agc ggg gtg ggc atc gac gag tgg tgg Gly Ile Leu Glu Met Arg Trp Ser Gly Val Gly Ile Asp Glu Trp Trp 905 910 915	3091
agg aac gag cag ttc tgg gtg atc ggg ggc atc tcc gcg cac ctc ttc Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Ile Ser Ala His Leu Phe 920 925 930	3139
gcc gtg ttc cag ggc ctg ctc aag gtg ctg gcc ggc atc gac acc aac Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile Asp Thr Asn 935 940 945 950	3187
ttc acc gtc acc tcc aag gcc tcc gac gag gac ggc gac ttc gcg gag Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp Phe Ala Glu 955 960 965	3235
ctg tac atg ttc aag tgg acg acg ctc ctg atc ccg ccc acc acc atc Leu Tyr Met Phe Lys Trp Thr Thr Leu Leu Ile Pro Pro Thr Thr Ile 970 975 980	3283
ctg atc atc aac ctg gtc ggc gtc gtc gcc ggc atc tcc tac gcc atc Leu Ile Ile Asn Leu Val Gly Val Val Ala Gly Ile Ser Tyr Ala Ile 985 990 995	3331
aac agc gga tac cag tcg tgg ggc ccg ctc ttc ggc aag ctc ttc ttc Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys Leu Phe Phe 1000 1005 1010	3379
gcc ttc tgg gtc atc gtc cac ctg tac ccg ttc ctc aag ggc ctc atg Ala Phe Trp Val Ile Val His Leu Tyr Pro Phe Leu Lys Gly Leu Met 1015 1020 1025 1030	3427
ggc agg cag aac ccg acc ccg acc atc gtc gtc gtc tgg gcc atc ctg Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Val Val Trp Ala Ile Leu 1035 1040 1045	3475
ctg gcg tcc atc ttc tcc ttg ctg tgg gtt cgc atc gac ccc ttc acc Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Arg Ile Asp Pro Phe Thr 1050 1055 1060	3523
acc ccg gtc act ggc ccg gat acc cag acg tgt ggc atc aac t Thr Arg Val Thr Gly Pro Asp Thr Gln Thr Cys Gly Ile Asn 1065 1070 1075	3566
gctaggaaag tggaaggttt gtactttgtta gaaacggagg aataaccacgt gccatctgtt gtctgttaag ttatatatata ataagcagca agtggcgta tttacagcta cgtacagacc agtggatatt gtttaccaca aagttttact tgtgttaata tgcattttt tggttatata aaaaaaaaaaaaaaa aaaaaaaaaaaaaaggc cgccccgc	3626 3686 3746 3773

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<212> PRT
<213> Zea mays

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Asp Val Phe Ala Ala Cys Asp Val Cys Gly Phe Pro Val Cys Arg Pro
35 40 45
Cys Tyr Glu Tyr Glu Arg Lys Asp Gly Thr Gln Ala Cys Pro Gln Cys
50 55 60
Lys Thr Lys Tyr Lys Arg His Lys Gly Ser Pro Ala Ile Arg Gly Glu
65 70 75 80
Glu Gly Asp Asp Thr Asp Ala Asp Ser Asp Phe Asn Tyr Leu Ala Ser
85 90 95
Gly Asn Glu Asp Gln Lys Gln Lys Ile Ala Asp Arg Met Arg Ser Trp
100 105 110
Arg Met Asn Val Gly Gly Ser Gly Asp Val Gly Arg Pro Lys Tyr Asp
115 120 125
Ser Gly Glu Ile Gly Leu Thr Lys Tyr Asp Ser Gly Glu Ile Pro Arg
130 135 140
Gly Tyr Ile Pro Ser Val Thr Asn Ser Gln Ile Ser Gly Glu Ile Pro
145 150 155 160
Gly Ala Ser Pro Asp His His Met Met Ser Pro Thr Gly Asn Ile Gly
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Lys Arg Ala Pro Phe Pro Tyr Val Asn His Ser Pro Asn Pro Ser Arg
180 185 190
Glu Phe Ser Gly Ser Ile Gly Asn Val Ala Trp Lys Glu Arg Val Asp
195 200 205
Gly Trp Lys Met Lys Gln Asp Lys Gly Thr Ile Pro Met Thr Asn Gly
210 215 220
Thr Ser Ile Ala Pro Ser Glu Gly Arg Gly Val Gly Asp Ile Asp Ala
225 230 235 240
Ser Thr Asp Tyr Asn Met Glu Asp Ala Leu Leu Asn Asp Glu Thr Arg
245 250 255
Gln Pro Leu Ser Arg Lys Val Pro Leu Pro Ser Ser Arg Ile Asn Pro
260 265 270
Tyr Arg Met Val Ile Val Leu Arg Leu Ile Val Leu Ser Ile Phe Leu
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His Tyr Arg Ile Thr Asn Pro Val Arg Asn Ala Tyr Pro Leu Trp Leu
290 295 300
Leu Ser Val Ile Cys Glu Ile Trp Phe Ala Leu Ser Trp Ile Leu Asp
305 310 315 320
Gln Phe Pro Lys Trp Phe Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg
325 330 335
Leu Ala Leu Arg Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Ala
340 345 350
Val Asp Ile Phe Val Ser Thr Val Asp Pro Met Lys Glu Pro Pro Leu
355 360 365
Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val
370 375 380
Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ala Ala Met Leu Thr
385 390 395 400
Phe Asp Ala Leu Ala Glu Thr Ser Glu Phe Ala Arg Lys Trp Val Pro
405 410 415

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Phe Val Lys Lys Tyr Asn Ile Glu Pro Arg Ala Pro Glu Trp Tyr Phe
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 Ser Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val His Pro Ser Phe Val
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 Lys Asp Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg
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 Val Asn Gly Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp
 465 470 475 480
 Ile Met Gln Asp Gly Thr Pro Trp Pro Gly Asn Asn Thr Xaa Asp His
 485 490 495
 Pro Gly Met Ile Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr
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 Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg
 515 520 525
 Pro Gly Phe Gln His His Lys Lys Ala Gly Ala Met Asn Ala Leu Val
 530 535 540
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 545 550 555 560
 Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Leu Arg Glu Ala Met Cys
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 Phe Leu Met Asp Pro Asn Leu Gly Arg Ser Val Cys Tyr Val Gln Phe
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 Pro Gln Arg Phe Asp Gly Ile Asp Arg Asn Asp Arg Tyr Ala Asn Arg
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 Asn Thr Val Phe Phe Asp Ile Asn Leu Arg Gly Leu Asp Gly Ile Gln
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 Tyr Gly Tyr Glu Pro Pro Ile Lys Gln Lys Lys Gly Gly Phe Leu Ser
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 Ser Leu Cys Gly Gly Arg Lys Lys Ala Ser Lys Ser Lys Lys Gly Ser
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 Asp Lys Lys Lys Ser Gln Lys His Val Asp Ser Ser Val Pro Val Phe
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 Asn Leu Glu Asp Ile Glu Glu Gly Val Glu Gly Ala Gly Phe Asp Asp
 690 695 700
 Glu Lys Ser Leu Leu Met Ser Gln Met Ser Leu Glu Lys Arg Phe Gly
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 Gln Ser Ala Ala Phe Val Ala Ser Thr Leu Met Glu Tyr Gly Gly Val
 725 730 735
 Pro Gln Ser Ala Thr Pro Glu Ser Leu Leu Lys Glu Ala Ile His Val
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 Ile Ser Cys Gly Tyr Glu Asp Lys Thr Glu Trp Gly Thr Glu Ile Gly
 755 760 765
 Trp Ile Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met
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 His Ala Arg Gly Trp Arg Ser Ile Tyr Cys Met Pro Lys Arg Pro Ala
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 Phe Lys Gly Ser Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val
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 820 825 830
 Pro Leu Trp Tyr Gly Tyr Gly Arg Leu Lys Phe Leu Glu Arg Phe
 835 840 845
 Ala Tyr Ile Asn Thr Thr Ile Tyr Pro Leu Thr Ser Ile Pro Leu Leu
 850 855 860
 Ile Tyr Cys Ile Leu Pro Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile
 865 870 875 880

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Ile Pro Glu Ile Ser Asn Phe Ala Ser Ile Trp Phe Ile Ser Leu Phe
 885 890 895
 Ile Ser Ile Phe Ala Thr Gly Ile Leu Glu Met Arg Trp Ser Gly Val
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 Gly Ile Asp Glu Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly
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 Ile Ser Ala His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu
 930 935 940
 Ala Gly Ile Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu
 945 950 955 960
 Asp Gly Asp Phe Ala Glu Leu Tyr Met Phe Lys Trp Thr Thr Leu Leu
 965 970 975
 Ile Pro Pro Thr Thr Ile Leu Ile Ile Asn Leu Val Gly Val Val Ala
 980 985 990
 Gly Ile Ser Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu
 995 1000 1005
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 Val Val Trp Ala Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val
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 Cys Gly Ile Asn Cys
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tggtctccgc	ccgcctcgtc	ggtgttggtg	tctgttggcgt	gtggagccgt	ctcggtggaa	180

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gcagcggggaa	gggagcggag	atg	gcg	gcc	aac	aag	ggg	atg	gtg	gct	ggc	tcg	233			
		Met	Ala	Ala	Asn	Lys	Gly	Met	Val	Ala	Gly	Ser				
1		5										10				
cac	aac	cgc	aac	gag	ttc	gtc	atg	atc	cgc	cac	gac	ggc	gat	gtg	ccg	281
His	Asn	Arg	Asn	Glu	Phe	Val	Met	Ile	Arg	His	Asp	Gly	Asp	Val	Pro	
15		20											25			
ggc	tcg	gct	aag	ccc	aca	aag	agt	gct	aat	gga	cag	gtc	tgc	cag	att	329
Gly	Ser	Ala	Lys	Pro	Thr	Lys	Ser	Ala	Asn	Gly	Gln	Val	Cys	Gln	Ile	
30		35											40			
tgc	ggt	gac	tct	gtg	ggt	gtt	tca	gcc	act	ggt	gat	gtc	ttt	gtt	gcc	377
Cys	Gly	Asp	Ser	Val	Gly	Val	Ser	Ala	Thr	Gly	Asp	Val	Phe	Val	Ala	
45		50											55			
tgc	aat	gag	tgt	gcc	ttc	cct	gtc	tgc	cgc	cca	tgc	tat	gag	tat	gag	425
Cys	Asn	Glu	Cys	Ala	Phe	Pro	Val	Cys	Arg	Pro	Cys	Tyr	Glu	Tyr	Glu	
60		65											75			
cgc	aag	gag	ggg	aac	caa	tgc	tgc	ccc	cag	tgc	aag	act	aga	tac	aag	473
Arg	Lys	Glu	Gly	Asn	Gln	Cys	Cys	Pro	Gln	Cys	Lys	Thr	Arg	Tyr	Lys	
80		85											90			
aga	cag	aaa	ggt	agc	cct	cga	gtt	cat	ggt	gat	gag	gat	gag	gaa	gat	521
Arg	Gln	Lys	Gly	Ser	Pro	Arg	Val	His	Gly	Asp	Glu	Asp	Glu	Glu	Asp	
95		100											105			
gtt	gat	gac	cta	gac	aat	gaa	ttc	aac	tac	aag	caa	ggc	agt	ggg	aaa	569
Val	Asp	Asp	Leu	Asp	Asn	Glu	Phe	Asn	Tyr	Lys	Gln	Gly	Ser	Gly	Lys	
110		115											120			
ggc	cca	gag	tgg	caa	ctg	caa	gga	gat	gat	gct	gat	ctg	tct	tca	tct	617
Gly	Pro	Glu	Trp	Gln	Leu	Gln	Gly	Asp	Asp	Ala	Asp	Leu	Ser	Ser	Ser	
125		130											135			
gct	cgc	cat	gag	cca	cat	cat	cgg	att	cca	cgc	ctg	aca	agc	ggt	caa	665
Ala	Arg	His	Glu	Pro	His	His	Arg	Ile	Pro	Arg	Leu	Thr	Ser	Gly	Gln	
140		145											150		155	
cag	ata	tct	gga	gag	att	cct	gat	gct	tcc	cct	gac	cgt	cat	tct	atc	713
Gln	Ile	Ser	Gly	Glu	Ile	Pro	Asp	Ala	Ser	Pro	Asp	Arg	His	Ser	Ile	
160		165											170			
cgc	agt	cca	aca	tcg	agc	tat	gtt	gat	cca	agc	gtc	cca	gtt	cct	gtg	761
Arg	Ser	Pro	Thr	Ser	Ser	Tyr	Val	Asp	Pro	Ser	Val	Pro	Val	Pro	Val	
175		180											185			
agg	att	gtg	gac	ccc	tcg	aag	gac	ttg	aat	tcc	tat	ggg	ctt	aat	agt	809
Arg	Ile	Val	Asp	Pro	Ser	Lys	Asp	Leu	Asn	Ser	Tyr	Gly	Ieu	Asn	Ser	
190		195											200			
gtt	gac	tgg	aag	aga	gtt	gag	agc	tgg	agg	gtt	aaa	cag	gac	aaa	857	
Val	Asp	Trp	Lys	Glu	Arg	Val	Glu	Ser	Tyr	Arg	Val	Lys	Gln	Asp	Lys	
205		210											215			
aat	atg	atg	caa	gtg	act	aat	aaa	tat	cca	gag	gct	aga	gga	gga	gac	905
Asn	Met	Met	Gln	Val	Thr	Asn	Lys	Tyr	Pro	Glu	Ala	Arg	Gly	Gly	Asp	

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220	225	230	235	
				953
atg gag ggg act ggc tca aat gga gaa nat atg caa atg gtt gat gat Met Glu Gly Thr Gly Ser Asn Gly Glu Xaa Met Gln Met Val Asp Asp				
240	245	250		
				1001
gca cgg cta cct ttg agc cgt atc gtg cca att tcc tca aac cag ctc Ala Arg Leu Pro Leu Ser Arg Ile Val Pro Ile Ser Ser Asn Gln Leu				
255	260	265		
				1049
aac ctt tac cgg gta gtg atc att ctc cgt ctt atc atc ctg tgc ttc Asn Leu Tyr Arg Val Val Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe				
270	275	280		
				1097
ttc ttc cag tat cgt gtc agt cat cca gtg cgt gat gct tat gga tta Phe Phe Gln Tyr Arg Val Ser His Pro Val Arg Asp Ala Tyr Gly Leu				
285	290	295		
				1145
tgg cta gta tct gtt atc tgc gag gtc tgg ttt gcc ttg tct tgg ctt Trp Leu Val Ser Val Ile Cys Glu Val Trp Phe Ala Leu Ser Trp Leu				
300	305	310	315	
				1193
cta gat cag ttc cca aaa tgg tat cca atc aac cgt gag aca tat ctt Leu Asp Gln Phe Pro Lys Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu				
320	325	330		
				1241
gac agg ctt gca ttg agg tat gat aga gag gga gag cca tca cag ctg Asp Arg Leu Ala Leu Arg Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu				
335	340	345		
				1289
gct ccc att gat gtc ttc gtc agt aca gtg gat cca ttg aag gaa cct Ala Pro Ile Asp Val Phe Val Ser Thr Val Asp Pro Leu Lys Glu Pro				
350	355	360		
				1337
cca ctg atc aca gcc aac act gtt ttg tcc att ctt tct gtg gat tac Pro Leu Ile Thr Ala Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr				
365	370	375		
				1385
cct gtt gac aaa gtg tca tgc tat gtt tct gat gat ggt tca gct atg Pro Val Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ser Ala Met				
380	385	390	395	
				1433
ctg act ttt gag tct ctc tca gaa acc gca gaa ttt gct aga aag tgg Leu Thr Phe Glu Ser Leu Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp				
400	405	410		
				1481
gtt ccc ttt tgt aag aag cac aat att gaa cca aga gct cca gaa ttt Val Pro Phe Cys Lys Lys His Asn Ile Glu Pro Arg Ala Pro Glu Phe				
415	420	425		
				1529
tac ttt gct caa aaa ata gat tac ctg aag gac aaa att caa cct tca Tyr Phe Ala Gln Lys Ile Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser				
430	435	440		
				1577
ttt gtt aag gaa aga cgc gca atg aag agg gag tat gaa gaa ttc aaa Phe Val Lys Glu Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys				
445	450	455		

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gta aga atc aat gcc ctt gtt gcc aaa gca cag aaa gtg cct gaa gag Val Arg Ile Asn Ala Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu 460 465 470 475	1625
ggg tgg acc atg gct gat gga act gca tgg cct ggg aat aat cct agg Gly Trp Thr Met Ala Asp Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg 480 485 490	1673
gac cat cct ggc atg att cag gtt ttc ttg ggg cac agt ggt ggg ctc Asp His Pro Gly Met Ile Gln Val Phe Leu Gly His Ser Gly Gly Leu 495 500 505	1721
gac act gat gga aat gag tta cca cgt ctt gtc tat gtc tct cgt gaa Asp Thr Asp Gly Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu 510 515 520	1769
aag aga cca ggc ttt cag cat cac aag aag gct ggt gca atg aat gcg Lys Arg Pro Gly Phe Gln His His Lys Lys Ala Gly Ala Met Asn Ala 525 530 535	1817
ctg att cgt gta tct gct gtg ctg aca aat ggt gcc tat ctt ctc aat Leu Ile Arg Val Ser Ala Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn 540 545 550 555	1865
gtg gat tgc gac cat tac ttc aat agc agc aaa gct ctt aga gaa gca Val Asp Cys Asp His Tyr Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala 560 565 570	1913
atg tgc ttc atg atg gat ccg gct cta gga agg aaa act tgt tat gta Met Cys Phe Met Met Asp Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val 575 580 585	1961
caa ttt cca cag aga ttt gat ggc att gac ttg cac gat cga tat gct Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Leu His Asp Arg Tyr Ala 590 595 600	2009
aat cgg aac ata gtt ttc ttt gat atc aac atg aaa ggt ctg gat ggc Asn Arg Asn Ile Val Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly 605 610 615	2057
att cag ggt cca gtt tac gtg gga aca gga tgc tgt ttc aat aga cag Ile Gln Gly Pro Val Tyr Val Gly Thr Gly Cys Cys Phe Asn Arg Gln 620 625 630 635	2105
gct ttg tat gga tac gat cct gtt ttg act gaa gct gat ctg gag cca Ala Leu Tyr Gly Tyr Asp Pro Val Leu Thr Glu Ala Asp Leu Glu Pro 640 645 650	2153
aac att gtt att aag agc tgc tgt ggt aga agg aag aaa aag aac aag Asn Ile Val Ile Lys Ser Cys Cys Gly Arg Arg Lys Lys Asn Lys 655 660 665	2201
agt tat atg gat agt caa agc cgt att atg aag aga aca gaa tct tca Ser Tyr Met Asp Ser Gln Ser Arg Ile Met Lys Arg Thr Glu Ser Ser 670 675 680	2249
gct ccc atc ttc aat atg gaa gac atc gaa gag ggt att gaa ggt tac Ala Pro Ile Phe Asn Met Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr	2297

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685	690	695	
gag gat gaa agg tca gtg ctt atg tcc cag agg aaa ttg gag aaa cgc Glu Asp Glu Arg Ser Val Leu Met Ser Gln Arg Lys Leu Glu Lys Arg 700 705 710 715			2345
ttt ggt cag tct cct att ttc att gca tcc acc ttt atg aca caa ggt Phe Gly Gln Ser Pro Ile Phe Ile Ala Ser Thr Phe Met Thr Gln Gly 720 725 730			2393
ggc ata cca cct tca aca aac cca gct tct cta cta aag gaa gct atc Gly Ile Pro Pro Ser Thr Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile 735 740 745			2441
cat gtc atc agt tgt gga tat gag gac aaa act gaa tgg gga aaa gag His Val Ile Ser Cys Gly Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu 750 755 760			2489
att ggc tgg atc tat ggt tca gta acg gag gat att ctg act ggg ttt Ile Gly Trp Ile Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe 765 770 775			2537
aaa atg cat gca agg ggc tgg caa tca atc tac tgc atg cca cca cga Lys Met His Ala Arg Gly Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg 780 785 790 795			2585
cct tgt ttc aag ggt tct gca cca atc aat ctt tcc gat cgt ctt aat Pro Cys Phe Lys Gly Ser Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn 800 805 810			2633
cag gtg ctc cgt tgg gct ctt ggg tca gtg gaa att ctg ctt agt aga Gln Val Leu Arg Trp Ala Leu Gly Ser Val Glu Ile Leu Leu Ser Arg 815 820 825			2681
cat tgt cct atc tgg tat ggt tac aat gga cga ttg aag ctt ttg gag His Cys Pro Ile Trp Tyr Gly Tyr Asn Gly Arg Leu Lys Leu Glu 830 835 840			2729
agg ctg gct tac atc aac act att gta tat cca atc aca tcc att ccg Arg Leu Ala Tyr Ile Asn Thr Ile Val Tyr Pro Ile Thr Ser Ile Pro 845 850 855			2777
ctt att gcc tat tgt gtg ctt ccc gct atc tgc ctc ctt acc aat aaa Leu Ile Ala Tyr Cys Val Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys 860 865 870 875			2825
ttt atc att cct gag att agc aat tat gct ggg atg ttc ttc att ctt Phe Ile Ile Pro Glu Ile Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu 880 885 890			2873
ctt ttc gcc tcc att ttt gcc act ggt ata ttg gag ctt aga tgg agt Leu Phe Ala Ser Ile Phe Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser 895 900 905			2921
ggg gtt ggc att gaa gat tgg tgg aga aat gag cag ttt tgg gtt att Gly Val Gly Ile Glu Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile 910 915 920			2969

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ggt ggc acc tct gcc cat ctc ttc gca gtg ttc cag ggt ctg ctg aaa		3017	
Gly Gly Thr Ser Ala His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys			
925	930	935	
gtg ttg gct ggg att gat acc aac ttc aca gtt acc tca aag gca tct		3065	
Val Leu Ala Gly Ile Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser			
940	945	950	955
gat gag gat ggc gac ttt gct gag cta tat gtg ttc aag tgg acc agt		3113	
Asp Glu Asp Gly Asp Phe Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser			
960	965	970	
ttg ctc att cct ccg acc act gtt ctt gtc att aac ctg gtc gga atg		3161	
Leu Leu Ile Pro Pro Thr Thr Val Leu Val Ile Asn Leu Val Gly Met			
975	980	985	
gtg gca gga att tct tat gcc att aac agt ggc tac caa tcc tgg ggt		3209	
Val Ala Gly Ile Ser Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly			
990	995	1000	
ccg ctc ttt gga aag ctg ttc tcg atc tgg gtg atc ctc cat ctc		3257	
Pro Leu Phe Gly Lys Leu Phe Phe Ser Ile Trp Val Ile Leu His Leu			
1005	1010	1015	
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Tyr Pro Phe Leu Lys Gly Leu Met Gly Arg Gln Asn Arg Thr Pro Thr			
1020	1025	1030	1035
atc gtc att gtc tgg tcc atc ctt ctt gca tct atc ttc tcc ttg ctg		3353	
Ile Val Ile Val Trp Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu			
1040	1045	1050	
tgg gtg aag atc gat cct ttc atc tcc ccg aca cag aaa gct gct gcc		3401	
Trp Val Lys Ile Asp Pro Phe Ile Ser Pro Thr Gln Lys Ala Ala Ala			
1055	1060	1065	
ttg ggg caa tgt ggc gtc aac t gctgatcgag acagtgactc ttatggaaag		3453	
Leu Gly Gln Cys Gly Val Asn			
1070			
aggctcaatc aagatctgcc ccctcggtgt aataacctgag gaggcttagat gggaaattcct		3513	
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Phe Val Met Ile Arg His Asp Gly Asp Val Pro Gly Ser Ala Lys Pro			
20 25 30			
Thr Lys Ser Ala Asn Gly Gln Val Cys Gln Ile Cys Gly Asp Ser Val			

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35	40	45
Gly Val Ser Ala Thr Gly Asp Val Phe Val Ala Cys Asn Glu Cys Ala		
50	55	60
Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Glu Gly Asn		
65	70	75
Gln Cys Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Gln Lys Gly Ser		
85	90	95
Pro Arg Val His Gly Asp Glu Asp Glu Glu Asp Val Asp Asp Leu Asp		
100	105	110
Asn Glu Phe Asn Tyr Lys Gln Gly Ser Gly Lys Gly Pro Glu Trp Gln		
115	120	125
Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ser Ala Arg His Glu Pro		
130	135	140
His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly Glu		
145	150	155
Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr Ser		
165	170	175
Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp Pro		
180	185	190
Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys Glu		
195	200	205
Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Met Gln Val		
210	215	220
Thr Asn Lys Tyr Pro Glu Ala Arg Gly Gly Asp Met Glu Gly Thr Gly		
225	230	235
Ser Asn Gly Glu Xaa Met Gln Met Val Asp Asp Ala Arg Leu Pro Leu		
245	250	255
Ser Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg Val		
260	265	270
Val Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe Phe Phe Gln Tyr Arg		
275	280	285
Val Ser His Pro Val Arg Asp Ala Tyr Gly Leu Trp Leu Val Ser Val		
290	295	300
Ile Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe Pro		
305	310	315
Lys Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu		
325	330	335
Arg Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp Val		
340	345	350
Phe Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr Ala		
355	360	365
Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr Pro Val Asp Lys Val		
370	375	380
Ser Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu Ser		
385	390	395
Leu Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys		
405	410	415
Lys His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln Lys		
420	425	430
Ile Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu Arg		
435	440	445
Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg Ile Asn Ala		
450	455	460
Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met Ala		
465	470	475
Asp Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met		
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Ile Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn		

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Gln His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser		
530	535	540
Ala Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His		
545	550	555
Tyr Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met		
565	570	575
Asp Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg		
580	585	590
Phe Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val		
595	600	605
Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val		
610	615	620
Tyr Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr		
625	630	635
Asp Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Ile Lys		
645	650	655
Ser Cys Cys Gly Arg Arg Lys Lys Lys Asn Lys Ser Tyr Met Asp Ser		
660	665	670
Gln Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn		
675	680	685
Met Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser		
690	695	700
Val Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro		
705	710	715
Ile Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser		
725	730	735
Thr Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys		
740	745	750
Gly Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr		
755	760	765
Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg		
770	775	780
Gly Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly		
785	790	795
Ser Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp		
805	810	815
Ala Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile Trp		
820	825	830
Tyr Gly Tyr Asn Gly Arg Leu Lys Leu Leu Glu Arg Leu Ala Tyr Ile		
835	840	845
Asn Thr Ile Val Tyr Pro Ile Thr Ser Ile Pro Leu Ile Ala Tyr Cys		
850	855	860
Val Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu		
865	870	875
Ile Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile		
885	890	895
Phe Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu		
900	905	910
Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala		
915	920	925
His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile		
930	935	940
Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp		
945	950	955
Phe Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro		

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965	970	975
Thr Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser		
980	985	990
Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys		
995	1000	1005
Leu Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys		
1010	1015	1020
Gly Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp		
1025	1030	1035
Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp		
1045	1050	1055
Pro Phe Ile Ser Pro Thr Gln Lys Ala Ala Ala Leu Gly Gln Cys Gly		
1060	1065	1070
Val Asn Cys		
1075		

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25

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25

<210> 13
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tggtgtggcggt cgctggcgct gcccgtcgga tctagagggc cgcacgggct gattccctc			120
cgccggcctc gtccgtgtcg gtggagtgtg aatcggtgtg tgttaggagga ggcggag			178
atg gcg gcc aac aag ggg atg gtg gca ggc tct cac aac cgc aac gag			226
Met Ala Ala Asn Lys Gly Met Val Ala Gly Ser His Asn Arg Asn Glu			
1	5	10	15

ttc gtc atg atc cgc cac gac ggc gac gcg cct gtc ccg gct aag ccc			274
Phe Val Met Ile Arg His Asp Gly Asp Ala Pro Val Pro Ala Lys Pro			
20	25	30	

acg aag agt gcg aat ggg cag gtc tgc cag att tgt ggc gac act gtt			322
Thr Lys Ser Ala Asn Gly Gln Val Cys Gln Ile Cys Gly Asp Thr Val			
35	40	45	

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ggc ttt tca gcc act ggt gat gtc ttt gtt gcc tgc aat gag tgt gcc 370
 Gly Val Ser Ala Thr Gly Asp Val Phe Val Ala Cys Asn Glu Cys Ala
 50 55 60

 ttc cct gtc tgc cgc cct tgc tat gag tac gag cgc aag gaa ggg aac 418
 Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Glu Gly Asn
 65 70 75 80

 caa tgc tgc cct cag tgc aag act aga tac aag aga cag aaa ggt agc 466
 Gln Cys Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Gln Lys Gly Ser
 85 90 95

 cct cga gtt cat ggt gat gat gag gag gaa gat gtt gat gac ctg gac 514
 Pro Arg Val His Gly Asp Asp Glu Glu Asp Val Asp Asp Leu Asp
 100 105 110

 aat gaa ttc aac tat aag caa ggc aat ggg aag ggc cca gag tgg cag 562
 Asn Glu Phe Asn Tyr Lys Gln Gly Asn Gly Lys Gly Pro Glu Trp Gln
 115 120 125

 ctt caa gga gat gac gct gat ctg tct tca tct gct cgc cat gac cca 610
 Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ser Ala Arg His Asp Pro
 130 135 140

 cac cat cgg att cca cgc ctt aca agt gga caa cag ata tct gga gag 658
 His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly Glu
 145 150 155 160

 atc cct gat gca tcc cct gac cgt cat tct atc cgc agt cca aca tcc 706
 Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr Ser
 165 170 175

 agc tat gtt gat cca agc gtt cca gtt cct gtg agg att gtg gac ccc 754
 Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp Pro
 180 185 190

 tcg aag gac ttg aat tcc tat ggg ctt aat agt gtt gac tgg aag gaa 802
 Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys Glu
 195 200 205

 aga gtt gag agc tgg agg gtt aaa cag gac aaa aat atg ttg caa gtg 850
 Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Leu Gln Val
 210 215 220

 act aat aaa tat cca gag gct aga gga gac atg gag ggg act ggc tca 898
 Thr Asn Lys Tyr Pro Glu Ala Arg Gly Asp Met Glu Gly Thr Gly Ser
 225 230 235 240

 aat gga gaa gat atg caa atg gtt gat gat gca cgc cta cct ttg agc 946
 Asn Gly Glu Asp Met Gln Met Val Asp Asp Ala Arg Leu Pro Leu Ser
 245 250 255

 cgc att gtg cca att tcc tca aac cag ctc aac ctt tac cgg ata gta 994
 Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg Ile Val
 260 265 270

 atc att ctc cgt ctt atc atc ctg tgc ttc ttc caa tat cgt atc 1042

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Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe Phe Phe Gln Tyr Arg Ile			
275	280	285	
agt cat cca gtg cgt aat gct tat gga ttg tgg cta gta tct gtt atc			1090
Ser His Pro Val Arg Asn Ala Tyr Gly Leu Trp Leu Val Ser Val Ile			
290	295	300	
tgt gag gtc tgg ttt gcc ttg tcc tgg ctt cta gat cag ttc cca aaa			1138
Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe Pro Lys			
305	310	315	320
tgg tat cca atc aac cgt gag aca tat ctc gac agg ctt gca ttg agg			1186
Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu Arg			
325	330	335	
tat gat aga gag gga gag cca tca cag ctg gct ccc att gat gtc ttt			1234
Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp Val Phe			
340	345	350	
gtc agt aca gtg gat cca ttg aag gaa cct cca ctg atc aca gcc aac			1282
Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr Ala Asn			
355	360	365	
act gtt ttg tcc att ctt gct gtg gat tac cct gtt gac aaa gtg tca			1330
Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val Asp Lys Val Ser			
370	375	380	
tgc tat gtt tct gat gat ggc tca gct atg ctg act ttt gag tct ctc			1378
Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu Ser Leu			
385	390	395	400
tct gaa act gcc gaa ttt gct aga aag tgg gtt ccc ttt tgt aag aag			1426
Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys Lys			
405	410	415	
cac aat att gaa cca aga gct cca gaa ttt tac ttt gct caa aaa ata			1474
His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln Lys Ile			
420	425	430	
gat tac ctg aag gac aaa att caa cct tca ttt gtt aag gaa aga cga			1522
Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu Arg Arg			
435	440	445	
gca atg aag aga gag tat gaa gaa ttc aaa ata aga atc aat gcc ctt			1570
Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Ile Arg Ile Asn Ala Leu			
450	455	460	
gtt gcc aaa gca cag aaa gtg cct gaa gag ggg tgg acc atg gct gat			1618
Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met Ala Asp			
465	470	475	480
gga act gct tgg cct ggg aat aac cct agg gac cat cct ggc atg att			1666
Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met Ile			
485	490	495	
cag gtg ttc ttg ggg cac agt ggt ggg ctt gac act gat gga aat gaa			1714
Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn Glu			
500	505	510	

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tta cca cgt ctt gtc tat gtc tct cgt gaa aag aga cca ggc ttt cag Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe Gln 515 520 525	1762
cat cac aag aag gct ggt gca atg aat gca ctg att cgt gta tct gct His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser Ala 530 535 540	1810
gtg ctg aca aat ggt gcc tat ctt ctc aat gtg gat tgt gac cat tac Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His Tyr 545 550 555 560	1858
ttc aat agc agc aaa gct ctt aga gaa gca atg tgc ttc atg atg gat Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met Asp 565 570 575	1906
cca gct cta gga agg aaa act tgt tat gta caa ttt cca caa aga ttt Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg Phe 580 585 590	1954
gat ggc att gac ttg cac gat cga tat gct aat agg aac ata gtc ttc Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val Phe 595 600 605	2002
ttt gat atc aac atg aaa ggt cta gat ggc att cag ggt cca gtc tat Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val Tyr 610 615 620	2050
gtg gga aca gga tgc tgt ttc aat agg cag gct ttg tat gga tat gat Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr Asp 625 630 635 640	2098
cct gtt ttg act gaa gct gat ctg gaa cct aac att gtt gtt aag agc Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Val Lys Ser 645 650 655	2146
tgc tgt ggt aga agg aag aga aag aac aag agt tat atg gat agt caa Cys Cys Gly Arg Arg Lys Arg Lys Asn Lys Ser Tyr Met Asp Ser Gln 660 665 670	2194
agc cgt att atg aag aga aca gaa tct tca gct ccc atc ttt aac atg Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn Met 675 680 685	2242
gaa gac atc gag gag ggt att gaa ggt tat gag gat gaa agg tca gtg Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser Val 690 695 700	2290
ctt atg tcc cag agg aaa ttg gag aaa cgc ttt ggt cag tct cca atc Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro Ile 705 710 715 720	2338
ttc att gca tcc acc ttt atg actcaa ggt ggc ata cca cct tca aca Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser Thr 725 730 735	2386
aac cca gct tct cta ctg aag gaa gct atc cat gtt atc agc tgt ggg	2434

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Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly			
740	745	750	
tac gag gac aaa act gaa tgg gga aaa gag att ggc tgg atc tat ggt			2482
Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly			
755	760	765	
tca gtt aca gag gat att ctg act ggg ttt aaa atg cat gca aga ggc			2530
Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg Gly			
770	775	780	
tgg caa tca atc tac tgc atg cca cca cga cct tgt ttc aag ggt tct			2578
Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly Ser			
785	790	795	800
gca cca atc aat ctt tct gat cgt ctt aat cag gtg ctc cgt tgg gct			2626
Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp Ala			
805	810	815	
ctt ggg tca gtg gaa att ctg ctt agc aga cat tgt cct ata tgg tat			2674
Leu Gly Ser Val Glu Ile Leu Ser Arg His Cys Pro Ile Trp Tyr			
820	825	830	
ggc tac aat ggg cga ttg aag ctt ttg gag agg ctg gct tac att aac			2722
Gly Tyr Asn Gly Arg Leu Lys Leu Leu Glu Arg Leu Ala Tyr Ile Asn			
835	840	845	
acc att gtt tat cca atc aca tct gtt ccg ctt atc gcc tat tgt gtg			2770
Thr Ile Val Tyr Pro Ile Thr Ser Val Pro Leu Ile Ala Tyr Cys Val			
850	855	860	
ctt cct gct atc tgt ctt ctt acc aat aaa ttt atc att cct gag att			2818
Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu Ile			
865	870	875	880
agt aat tat gct gga atg ttc ttc att ctt ctt ttt gcc tcc att ttc			2866
Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile Phe			
885	890	895	
gca act ggt ata ttg gag ctc aga tgg agt ggt gtt ggc att gaa gat			2914
Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu Asp			
900	905	910	
tgg tgg aga aat gag cag ttt tgg gtt att ggt ggc acc tct gcc cat			2962
Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala His			
915	920	925	
ctc ttc gcg gtg ttc cag ggt ctg ctg aaa gtg ttg gct ggg att gat			3010
Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile Asp			
930	935	940	
acc aac ttc aca gtt acc tca aag gca tct gat gag gat ggc gac ttt			3058
Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp Phe			
945	950	955	960
gct gag cta tat gtg ttc aag tgg acc agt ttg ctc atc cct ccg acc			3106
Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro Thr			
965	970	975	

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act gtt ctt gtc att aac ctg gtc gga atg gtg gca gga att tcg tat 3154
Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser Tyr
980 985 990

gcc att aac agc ggc tac caa tcc tgg ggt ccg ctc ttt gga aag ctg 3202
 Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys Leu
 995 1000 1005

ttc ttc tcg atc tgg gtg atc ctc cat ctc tac ccc ttc ctc aag ggt
 Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys Gly
 1010 1015 1020

ctc atg ggc agg cag aac cgc acg cca aca atc gtc atc gtt tgg tcc 3298
 Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser
 1025 1030 1035 1040

atc ctc ctt gcg tct atc ttc tcc ttg ctg tgg gtg aag atc gat cct 3346
Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp Pro
1045 1050 1055

ttc atc tcc ccg aca cag aaa gct gcc gcc ttg ggg caa tgt ggt gtg 3394
 Phe Ile Ser Pro Thr Gln Lys Ala Ala Ala Leu Gly Gln Cys Gly Val
 1060 1065 1070

aac t gctgatccag attgtgactc ttatctgaag aggctcagcc aaagatctgc 3448
Asn

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tctgcatcca	agtttatgcct	ctgtttattta	gcttcttcgg	tgccgggtct	gctgcagaca	3568
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Phe	Val	Met	Ile	Arg	His	Asp	Gly	Asp	Ala	Pro	Val	Pro	Ala	Lys	Pro
										20				25	30
Thr	Lys	Ser	Ala	Asn	Gly	Gln	Val	Cys	Gln	Ile	Cys	Gly	Asp	Thr	Val
										35				40	45
Gly	Val	Ser	Ala	Thr	Gly	Asp	Val	Phe	Val	Ala	Cys	Asn	Glu	Cys	Ala
										50				55	60
Phe	Pro	Val	Cys	Arg	Pro	Cys	Tyr	Glu	Tyr	Glu	Arg	Lys	Glu	Gly	Asn
										65				70	75
Gln	Cys	Cys	Pro	Gln	Cys	Lys	Thr	Arg	Tyr	Lys	Arg	Gln	Lys	Gly	Ser
										85				90	95
Pro	Arg	Val	His	Gly	Asp	Asp	Glu	Glu	Glu	Asp	Val	Asp	Asp	Leu	Asp
										100				105	110
Asn	Glu	Phe	Asn	Tyr	Lys	Gln	Gly	Asn	Gly	Lys	Gly	Pro	Glu	Trp	Gln
										115				120	125
Leu	Gln	Gly	Asp	Asp	Ala	Asp	Leu	Ser	Ser	Ser	Ala	Arg	His	Asp	Pro

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130	135	140
His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly Glu		
145	150	155
Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr Ser		160
165	170	175
Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp Pro		
180	185	190
Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys Glu		
195	200	205
Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Leu Gln Val		
210	215	220
Thr Asn Lys Tyr Pro Glu Ala Arg Gly Asp Met Glu Gly Thr Gly Ser		
225	230	235
Asn Gly Glu Asp Met Gln Met Val Asp Asp Ala Arg Leu Pro Leu Ser		240
245	250	255
Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg Ile Val		
260	265	270
Ile Ile Leu Arg Leu Ile Ile Cys Phe Phe Phe Gln Tyr Arg Ile		
275	280	285
Ser His Pro Val Arg Asn Ala Tyr Gly Leu Trp Leu Val Ser Val Ile		
290	295	300
Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe Pro Lys		
305	310	315
Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu Arg		320
325	330	335
Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp Val Phe		
340	345	350
Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr Ala Asn		
355	360	365
Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val Asp Lys Val Ser		
370	375	380
Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu Ser Leu		
385	390	395
Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys Lys		400
405	410	415
His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln Lys Ile		
420	425	430
Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu Arg Arg		
435	440	445
Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Ile Arg Ile Asn Ala Leu		
450	455	460
Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met Ala Asp		
465	470	475
Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met Ile		480
485	490	495
Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn Glu		
500	505	510
Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe Gln		
515	520	525
His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser Ala		
530	535	540
Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His Tyr		
545	550	555
Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met Asp		560
565	570	575
Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg Phe		
580	585	590
Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val Phe		

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595	600	605
Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val Tyr		
610	615	620
Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr Asp		
625	630	635
640		
Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Val Lys Ser		
645	650	655
Cys Cys Gly Arg Arg Lys Arg Lys Asn Lys Ser Tyr Met Asp Ser Gln		
660	665	670
Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn Met		
675	680	685
Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser Val		
690	695	700
Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro Ile		
705	710	715
720		
Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser Thr		
725	730	735
Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly		
740	745	750
Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly		
755	760	765
Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg Gly		
770	775	780
Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly Ser		
785	790	795
800		
Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp Ala		
805	810	815
Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile Trp Tyr		
820	825	830
Gly Tyr Asn Gly Arg Leu Lys Leu Leu Glu Arg Leu Ala Tyr Ile Asn		
835	840	845
Thr Ile Val Tyr Pro Ile Thr Ser Val Pro Leu Ile Ala Tyr Cys Val		
850	855	860
Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu Ile		
865	870	875
880		
Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile Phe		
885	890	895
Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu Asp		
900	905	910
Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala His		
915	920	925
Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile Asp		
930	935	940
Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp Phe		
945	950	955
960		
Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro Thr		
965	970	975
Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser Tyr		
980	985	990
Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys Leu		
995	1000	1005
Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys Gly		
1010	1015	1020
Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser		
1025	1030	1035
1040		
Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp Pro		
1045	1050	1055
Phe Ile Ser Pro Thr Gln Lys Ala Ala Leu Gly Gln Cys Gly Val		

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1060

1065

1070

Asn Cys

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<400> 15

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 25

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<220>

<221> CDS

<222> (144) ... (3399)

<400> 17

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atgaggatct gctgcttagag tgagaggagc tacgttcagt atccctctgcc ttccgtccggcg	120
gcggaaagtgg aggggaggaa gcg atg gag ggc agc gcc ggg ctg gtg gcc ggc	173
Met Glu Ala Ser Ala Gly Leu Val Ala Gly	
1 5 10	

tcc cac aac cgc aac gag ctc gtc atc cgc cgc gac ggc gat ccc	221
Ser His Asn Arg Asn Glu Leu Val Val Ile Arg Arg Asp Gly Asp Pro	
15 20 25	

ggg ccg aag ccg ccg cgg gag cag aac ggg cag gtg tgc cag att tgc	269
Gly Pro Lys Pro Pro Arg Glu Gln Asn Gly Gln Val Cys Gln Ile Cys	
30 35 40	

ggc gac gac gtc ggc ctt gcc ccc ggc ggg gac ccc ttc gtg gcg tgc	317
Gly Asp Asp Val Gly Leu Ala Pro Gly Gly Asp Pro Phe Val Ala Cys	
45 50 55	

aac gag tgc gcc ttc ccc gtc tgc cgg gac tgc tac gaa tac gag cgc	365
Asn Glu Cys Ala Phe Pro Val Cys Arg Asp Cys Tyr Glu Tyr Glu Arg	
60 65 70	

cgg gag ggc acg cag aac tgc ccc cag tgc aag act cga tac aag cgc	413
Arg Glu Gly Thr Gln Asn Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg	
75 80 85 90	

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ctc aag ggc tgc caa cgt gtg acc ggt gac gag gag gag gac ggc gtc 461
 Leu Lys Gly Cys Gln Arg Val Thr Gly Asp Glu Glu Glu Asp Gly Val
 , 95 100 105

 gat gac ctg gac aac gag ttc aac tgg gac ggc cat gac tcg cag tct 509
 Asp Asp Leu Asp Asn Glu Phe Asn Trp Asp Gly His Asp Ser Gln Ser
 110 115 120

 gtg gcc gag tcc atg ctc tac ggc cac atg agc tac ggc cgt gga ggt 557
 Val Ala Glu Ser Met Leu Tyr Gly His Met Ser Tyr Gly Arg Gly Gly
 125 130 135

 gac cct aat ggc gcg cca caa gct ttc cag ctc aac ccc aat gtt cca 605
 Asp Pro Asn Gly Ala Pro Gln Ala Phe Gln Leu Asn Pro Asn Val Pro
 140 145 150

 ctc ctc acc aac ggg caa atg gtg gat gac atc cca ccg gag cag cac 653
 Leu Leu Thr Asn Gly Gln Met Val Asp Asp Ile Pro Pro Glu Gln His
 155 160 165 170

 gcg ctg gtg cct ttc atg ggt ggt ggg gga aag agg ata cat ccc 701
 Ala Leu Val Pro Ser Phe Met Gly Gly Gly Lys Arg Ile His Pro
 175 180 185

 ctt cct tat gcg gat ccc agc tta cct gtg caa ccc agg tct atg gac 749
 Leu Pro Tyr Ala Asp Pro Ser Leu Pro Val Gln Pro Arg Ser Met Asp
 190 195 200

 cca tcc aag gat ctt gct gca tat ggg tat ggt agt gtt gct tgg aag 797
 Pro Ser Lys Asp Leu Ala Ala Tyr Gly Tyr Gly Ser Val Ala Trp Lys
 205 210 215

 gaa cgg atg gag aat tgg aag cag aga caa gag agg atg cac cag acg 845
 Glu Arg Met Glu Asn Trp Lys Gln Arg Gln Glu Arg Met His Gln Thr
 220 225 230

 ggg aat gat ggt ggt gat gat ggt gac gat gct gat cta cca cta 893
 Gly Asn Asp Gly Gly Asp Asp Gly Asp Asp Ala Asp Leu Pro Leu
 235 240 245 250

 atg gat gaa gca aga caa caa ctg tcc agg aaa att cca ctt cca tca 941
 Met Asp Glu Ala Arg Gln Gln Leu Ser Arg Lys Ile Pro Leu Pro Ser
 255 260 265

 agc cag att aat cca tat agg atg att atc att att cgg ctt gtg gtt 989
 Ser Gln Ile Asn Pro Tyr Arg Met Ile Ile Ile Arg Leu Val Val
 270 275 280

 ttg ggg ttc ttc cac tac cga gtg atg cat ccg gtg aat gat gca 1037
 Leu Gly Phe Phe His Tyr Arg Val Met His Pro Val Asn Asp Ala
 285 290 295

 ttt gct ttg tgg ctc ata tct gtt atc tgt gaa atc tgg ttt gcc atg 1085
 Phe Ala Leu Trp Leu Ile Ser Val Ile Cys Glu Ile Trp Phe Ala Met
 300 305 310

 tct tgg att ctt gat caa ttc cca aag tgg ttc cct att gag aga gag 1133
 Ser Trp Ile Leu Asp Gln Phe Pro Lys Trp Phe Pro Ile Glu Arg Glu

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315	320	325	330	
act tac cta gac cgg ctg tca ctg agg ttc gac aag gaa ggc cag cca Thr Tyr Leu Asp Arg Leu Ser Leu Arg Phe Asp Lys Glu Gly Gln Pro				1181
335		340	345	
tct caa ctt gct cca att gat ttc ttt gtc agt acg gtt gat ccc tta Ser Gln Leu Ala Pro Ile Asp Phe Phe Val Ser Thr Val Asp Pro Leu				1229
350		355	360	
aag gaa cct cct ttg gtc aca aca aat act gtt cta tct atc ctt tcg Lys Glu Pro Pro Leu Val Thr Thr Asn Thr Val Leu Ser Ile Leu Ser				1277
365		370	375	
gtg gat tat cct gtt gat aag gtt tct tgc tat gtt tct gat gat ggt Val Asp Tyr Pro Val Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly				1325
380		385	390	
gct gca atg cta acg ttt gaa gca tta tct gaa aca tct gaa ttt gca Ala Ala Met Leu Thr Phe Glu Ala Leu Ser Glu Thr Ser Glu Phe Ala				1373
395		400	405	410
aag aaa tgg gtt cct ttc tgc aaa cgg tac aat att gaa cct cgc gct Lys Lys Trp Val Pro Phe Cys Lys Arg Tyr Asn Ile Glu Pro Arg Ala				1421
415		420		425
cca gag tgg tac ttc caa cag aag ata gac tac ttg aaa gac aag gtg Pro Glu Trp Tyr Phe Gln Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val				1469
430		435		440
gca gca aac ttt gtt agg gag agg aga gca atg aag aga gag tat gag Ala Ala Asn Phe Val Arg Glu Arg Arg Ala Met Lys Arg Glu Tyr Glu				1517
445		450		455
gaa ttc aag gtg aga atc aat gcc tta gtt gcc aaa gcc cag aaa gtt Glu Phe Lys Val Arg Ile Asn Ala Leu Val Ala Lys Ala Gln Lys Val				1565
460		465		470
cct gaa gaa gga tgg aca atg caa gat gga acc ccc tgg cct gga aac Pro Glu Glu Gly Trp Thr Met Gln Asp Gly Thr Pro Trp Pro Gly Asn				1613
475		480		485
490				490
aat gtt cgt gat cat cct gga atg att cag gtc ttc ctt ggc caa agc Asn Val Arg Asp His Pro Gly Met Ile Gln Val Phe Leu Gly Gln Ser				1661
495		500		505
gga ggc ctt gac tgt gag gga aat gaa ctg cca cga ttg gtt tat gtt Gly Gly Leu Asp Cys Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val				1709
510		515		520
tct aga gag aaa cga cca ggc tat aac cat cat aag aaa gct ggt gct Ser Arg Glu Lys Arg Pro Gly Tyr Asn His His Lys Lys Ala Gly Ala				1757
525		530		535
atg aat gca ttg gtc cga gtc tct gct gta cta aca aat gct cca tat Met Asn Ala Leu Val Arg Val Ser Ala Val Leu Thr Asn Ala Pro Tyr				1805
540		545		550

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ttg tta aac ttg gat tgt gat cac tac atc aac aac agc aag gct ata Leu Leu Asn Leu Asp Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Ile 555 560 565 570	1853
aag gaa gca atg tgt ttt atg atg gac cct tta cta gga aag aag gtt Lys Glu Ala Met Cys Phe Met Met Asp Pro Leu Leu Gly Lys Lys Val 575 580 585	1901
tgc tat gta cag ttc cct caa aga ttt gat ggg att gat cgc cat gac Cys Tyr Val Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Arg His Asp 590 595 600	1949
cga tat gct aac cgg aat gtt gtc ttt ttt gat atc aac atg aaa ggt Arg Tyr Ala Asn Arg Asn Val Val Phe Phe Asp Ile Asn Met Lys Gly 605 610 615	1997
ttg gat ggt att cag ggt cca att tat gtt ggt act gga tgt gta ttt Leu Asp Gly Ile Gln Gly Pro Ile Tyr Val Gly Thr Gly Cys Val Phe 620 625 630	2045
aga agg cag gca tta tat ggt tat gat gcc ccc aaa aca aag aag cca Arg Arg Gln Ala Leu Tyr Gly Tyr Asp Ala Pro Lys Thr Lys Lys Pro 635 640 645 650	2093
cca tca agg act tgc aac tgc tgg ccc aag tgg tgc ttt tgc tgt tgc Pro Ser Arg Thr Cys Asn Cys Trp Pro Lys Trp Cys Phe Cys Cys Cys 655 660 665	2141
tgc ttt ggc aat agg aag caa aag aag act acc aaa ccc aaa aca gag Cys Phe Gly Asn Arg Lys Gln Lys Lys Thr Thr Lys Pro Lys Thr Glu 670 675 680	2189
aag aaa aag tta tta ttt ttc aag aaa gaa gag aac caa tcc cct gca Lys Lys Lys Leu Leu Phe Phe Lys Lys Glu Glu Asn Gln Ser Pro Ala 685 690 695	2237
tat gct ctt ggt gaa att gac gaa gct gct cca gga gct gag aat gaa Tyr Ala Leu Gly Glu Ile Asp Glu Ala Ala Pro Gly Ala Glu Asn Glu 700 705 710	2285
aag gcc ggt att gta aat caa caa aaa tta gaa aag aaa ttt ggc caa Lys Ala Gly Ile Val Asn Gln Gln Lys Leu Glu Lys Lys Phe Gly Gln 715 720 725 730	2333
tct tct gtt ttt gtt aca tcc aca ctt ctc gag aat ggt gga acc ttg Ser Ser Val Phe Val Thr Ser Thr Leu Leu Glu Asn Gly Gly Thr Leu 735 740 745	2381
aag agt gca agt cct gct tct ctt ttg aaa gaa gct ata cat gtc att Lys Ser Ala Ser Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile 750 755 760	2429
agt tgt ggt tat gaa gac aag aca gac tgg gga aaa gag att ggc tgg Ser Cys Gly Tyr Glu Asp Lys Thr Asp Trp Gly Lys Glu Ile Gly Trp 765 770 775	2477
atc tat gga tca gtt aca gaa gat att cta act ggt ttc aag atg cat Ile Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His	2525

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780	785	790	
tgt cat ggt tgg cgg tca att tac tgc ata cct aaa cgg gtt gca ttc Cys His Gly Trp Arg Ser Ile Tyr Cys Ile Pro Lys Arg Val Ala Phe 795 800 805 810			2573
aaa ggt tct gca cct ctg aat ctt tca gat cgt ctt cac cag gtg ctt Lys Gly Ser Ala Pro Leu Asn Leu Ser Asp Arg Leu His Gln Val Leu 815 820 825			2621
cgg tgg gct ctt ggg tct att gag atc ttc ttc agc aat cat tgc cct Arg Trp Ala Leu Gly Ser Ile Glu Ile Phe Phe Ser Asn His Cys Pro 830 835 840			2669
ctt tgg tat ggg tat ggt ggc ggt ctg aaa ttt ttg gaa aga ttt tcc Leu Trp Tyr Gly Tyr Gly Gly Leu Lys Phe Leu Glu Arg Phe Ser 845 850 855			2717
tac atc aac tcc atc gtg tat cct tgg aca tct att ccc ctc ttg gct Tyr Ile Asn Ser Ile Val Tyr Pro Trp Thr Ser Ile Pro Leu Leu Ala 860 865 870			2765
tac tgt aca ttg cct gcc atc tgt tta ttg aca ggg aaa ttt atc act Tyr Cys Thr Leu Pro Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile Thr 875 880 885 890			2813
cca gag ctg aat aat gtt gcc agc ctg tgg ttc atg tca ctt ttt atc Pro Glu Leu Asn Asn Val Ala Ser Leu Trp Phe Met Ser Leu Phe Ile 895 900 905			2861
tgc att ttt gct acg agc atc cta gaa atg aga tgg agt ggt gtt gga Cys Ile Phe Ala Thr Ser Ile Leu Glu Met Arg Trp Ser Gly Val Gly 910 915 920			2909
att gat gac tgg tgg agg aat gag cag ttc tgg gtc att gga ggt gtg Ile Asp Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Val 925 930 935			2957
tcc tca cac ctc ttt gct gtg ttc cag gga ctt ctc aag gtc ata gct Ser Ser His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Ile Ala 940 945 950			3005
ggt gtt gat aca agc ttc acc gtg aca tca aag ggt gga gat gat gag Gly Val Asp Thr Ser Phe Thr Val Thr Ser Lys Gly Gly Asp Asp Glu 955 960 965 970			3053
gag ttc tca gag cta tat aca ttc aaa tgg act acc tta ttg ata cct Glu Phe Ser Glu Leu Tyr Thr Phe Lys Trp Thr Thr Leu Leu Ile Pro 975 980 985			3101
cct acc acc ttg ctt cta ttg aac ttc att ggt gtg gtc gct ggc gtt Pro Thr Thr Leu Leu Leu Asn Phe Ile Gly Val Val Ala Gly Val 990 995 1000			3149
tca aat gcg atc aat aac gga tat gag tca tgg ggc ccc ctc ttt ggg Ser Asn Ala Ile Asn Asn Gly Tyr Glu Ser Trp Gly Pro Leu Phe Gly 1005 1010 1015			3197

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aag cta ttc ttt gca ttt tgg gtg att gtc cat ctt tat ccc ttt ctc Lys Leu Phe Phe Ala Phe Trp Val Ile Val His Leu Tyr Pro Phe Leu 1020 1025 1030	3245
aaa ggt ttg gtt gga agg caa aac agg aca cca acg att gtc atc gtc Lys Gly Leu Val Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val 1035 1040 1045 1050	3293
tgg tcc att ctg ctg gct tca atc ttc tcg ctc ctt tgg gtt cggtt att Trp Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Arg Ile 1055 1060 1065	3341
gat cct ttc ctt gcg aag gat gat ggt ccg ctt ctt gag gag tgg tgg Asp Pro Phe Leu Ala Lys Asp Asp Gly Pro Leu Leu Glu Glu Cys Gly 1070 1075 1080	3389
ttg gat tgc a actaggatgt cagtgcata cgtccccaa tctgcataatg Leu Asp Cys 1085	3439
cttgaagtat attttcttgtt gtttgcctttt atattcagtg tctgttagata agagacatga aatgtcccaa gtttctttt atccatgtg aacctactt atatctgaga gatatactgg gggaaaaatgg aggctgcggc aatccttgc cagttgggcc gtgaaataca gcataatgca gtgtttgatt gtgcagcatt ctttattact tggcgcaat atagatgggc tgagccgaac agcaaggtat ttgttattctg cactgctccc gtgtacaaac ttggttctca ataaggcagg caggaatgca tctgcctgtt gaacagagca acctgcacat tatttatgtt tgcctgttca ttggagggtt tggcattttc atgttcgtct atactagaaa aaacagaata ttagcattaa tctatagttt attaaatgttta attaaatgcgc ctgtttttt ttgtgtactt taatcatctg agttggttt gtgaa 3499 3559 3619 3679 3739 3799 3859 3919 3969	
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Met	Gly	Gly	Gly	Gly	Lys	Arg	Ile	His	Pro	Leu	Pro	Tyr	Ala	Asp	Pro
180							185						190		
Ser	Leu	Pro	Val	Gln	Pro	Arg	Ser	Met	Asp	Pro	Ser	Lys	Asp	Leu	Ala
195							200					205			
Ala	Tyr	Gly	Tyr	Gly	Ser	Val	Ala	Trp	Lys	Glu	Arg	Met	Glu	Asn	Trp
210							215					220			
Lys	Gln	Arg	Gln	Glu	Arg	Met	His	Gln	Thr	Gly	Asn	Asp	Gly	Gly	Gly
225							230			235			240		
Asp	Asp	Gly	Asp	Asp	Ala	Asp	Leu	Pro	Leu	Met	Asp	Glu	Ala	Arg	Gln
245							250					255			
Gln	Leu	Ser	Arg	Lys	Ile	Pro	Leu	Pro	Ser	Ser	Gln	Ile	Asn	Pro	Tyr
260							265					270			
Arg	Met	Ile	Ile	Ile	Ile	Arg	Leu	Val	Val	Leu	Gly	Phe	Phe	Phe	His
275							280					285			
Tyr	Arg	Val	Met	His	Pro	Val	Asn	Asp	Ala	Phe	Ala	Leu	Trp	Leu	Ile
290							295					300			
Ser	Val	Ile	Cys	Glu	Ile	Trp	Phe	Ala	Met	Ser	Trp	Ile	Leu	Asp	Gln
305							310				315			320	
Phe	Pro	Lys	Trp	Phe	Pro	Ile	Glu	Arg	Glu	Thr	Tyr	Leu	Asp	Arg	Leu
325							330					335			
Ser	Leu	Arg	Phe	Asp	Lys	Glu	Gly	Gln	Pro	Ser	Gln	Leu	Ala	Pro	Ile
340							345					350			
Asp	Phe	Phe	Val	Ser	Thr	Val	Asp	Pro	Leu	Lys	Glu	Pro	Pro	Leu	Val
355							360					365			
Thr	Thr	Asn	Thr	Val	Leu	Ser	Ile	Leu	Ser	Val	Asp	Tyr	Pro	Val	Asp
370							375					380			
Lys	Val	Ser	Cys	Tyr	Val	Ser	Asp	Asp	Gly	Ala	Ala	Met	Leu	Thr	Phe
385							390				395			400	
Glu	Ala	Leu	Ser	Glu	Thr	Ser	Glu	Phe	Ala	Lys	Lys	Trp	Val	Pro	Phe
405							410					415			
Cys	Lys	Arg	Tyr	Asn	Ile	Glu	Pro	Arg	Ala	Pro	Glu	Trp	Tyr	Phe	Gln
420							425					430			
Gln	Lys	Ile	Asp	Tyr	Leu	Lys	Asp	Lys	Val	Ala	Ala	Asn	Phe	Val	Arg
435							440					445			
Glu	Arg	Arg	Ala	Met	Lys	Arg	Glu	Tyr	Glu	Glu	Phe	Lys	Val	Arg	Ile
450							455					460			
Asn	Ala	Leu	Val	Ala	Lys	Ala	Gln	Lys	Val	Pro	Glu	Glu	Gly	Trp	Thr
465							470				475			480	
Met	Gln	Asp	Gly	Thr	Pro	Trp	Pro	Gly	Asn	Asn	Val	Arg	Asp	His	Pro
485							490					495			
Gly	Met	Ile	Gln	Val	Phe	Leu	Gly	Gln	Ser	Gly	Gly	Leu	Asp	Cys	Glu
500							505					510			
Gly	Asn	Glu	Leu	Pro	Arg	Leu	Val	Tyr	Val	Ser	Arg	Glu	Lys	Arg	Pro
515							520					525			
Gly	Tyr	Asn	His	His	Lys	Lys	Ala	Gly	Ala	Met	Asn	Ala	Leu	Val	Arg
530							535					540			
Val	Ser	Ala	Val	Leu	Thr	Asn	Ala	Pro	Tyr	Leu	Leu	Asn	Leu	Asp	Cys
545							550				555			560	
Asp	His	Tyr	Ile	Asn	Asn	Ser	Lys	Ala	Ile	Lys	Glu	Ala	Met	Cys	Phe
565							570					575			
Met	Met	Asp	Pro	Leu	Leu	Gly	Lys	Lys	Val	Cys	Tyr	Val	Gln	Phe	Pro
580							585					590			
Gln	Arg	Phe	Asp	Gly	Ile	Asp	Arg	His	Asp	Arg	Tyr	Ala	Asn	Arg	Asn
595							600					605			
Val	Val	Phe	Phe	Asp	Ile	Asn	Met	Lys	Gly	Leu	Asp	Gly	Ile	Gln	Gly
610							615					620			
Pro	Ile	Tyr	Val	Gly	Thr	Gly	Cys	Val	Phe	Arg	Arg	Gln	Ala	Leu	Tyr
625							630				635			640	

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Gly Tyr Asp Ala Pro Lys Thr Lys Lys Pro Pro Ser Arg Thr Cys Asn
 645 650 655
 Cys Trp Pro Lys Trp Cys Phe Cys Cys Cys Cys Phe Gly Asn Arg Lys
 660 665 670
 Gln Lys Lys Thr Thr Lys Pro Lys Thr Glu Lys Lys Leu Leu Phe
 675 680 685
 Phe Lys Lys Glu Glu Asn Gln Ser Pro Ala Tyr Ala Leu Gly Glu Ile
 690 695 700
 Asp Glu Ala Ala Pro Gly Ala Glu Asn Glu Lys Ala Gly Ile Val Asn
 705 710 715 720
 Gln Gln Lys Leu Glu Lys Lys Phe Gly Gln Ser Ser Val Phe Val Thr
 725 730 735
 Ser Thr Leu Leu Glu Asn Gly Gly Thr Leu Lys Ser Ala Ser Pro Ala
 740 745 750
 Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly Tyr Glu Asp
 755 760 765
 Lys Thr Asp Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly Ser Val Thr
 770 775 780
 Glu Asp Ile Leu Thr Gly Phe Lys Met His Cys His Gly Trp Arg Ser
 785 790 795 800
 Ile Tyr Cys Ile Pro Lys Arg Val Ala Phe Lys Gly Ser Ala Pro Leu
 805 810 815
 Asn Leu Ser Asp Arg Leu His Gln Val Leu Arg Trp Ala Leu Gly Ser
 820 825 830
 Ile Glu Ile Phe Phe Ser Asn His Cys Pro Leu Trp Tyr Gly Tyr Gly
 835 840 845
 Gly Gly Leu Lys Phe Leu Glu Arg Phe Ser Tyr Ile Asn Ser Ile Val
 850 855 860
 Tyr Pro Trp Thr Ser Ile Pro Leu Leu Ala Tyr Cys Thr Leu Pro Ala
 865 870 875 880
 Ile Cys Leu Leu Thr Gly Lys Phe Ile Thr Pro Glu Leu Asn Asn Val
 885 890 895
 Ala Ser Leu Trp Phe Met Ser Leu Phe Ile Cys Ile Phe Ala Thr Ser
 900 905 910
 Ile Leu Glu Met Arg Trp Ser Gly Val Gly Ile Asp Asp Trp Trp Arg
 915 920 925
 Asn Glu Gln Phe Trp Val Ile Gly Gly Val Ser Ser His Leu Phe Ala
 930 935 940
 Val Phe Gln Gly Leu Leu Lys Val Ile Ala Gly Val Asp Thr Ser Phe
 945 950 955 960
 Thr Val Thr Ser Lys Gly Gly Asp Asp Glu Glu Phe Ser Glu Leu Tyr
 965 970 975
 Thr Phe Lys Trp Thr Leu Leu Ile Pro Pro Thr Thr Leu Leu Leu
 980 985 990
 Leu Asn Phe Ile Gly Val Val Ala Gly Val Ser Asn Ala Ile Asn Asn
 995 1000 1005
 Gly Tyr Glu Ser Trp Gly Pro Leu Phe Gly Lys Leu Phe Phe Ala Phe
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 Trp Val Ile Val His Leu Tyr Pro Phe Leu Lys Gly Leu Val Gly Arg
 1025 1030 1035 1040
 Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser Ile Leu Leu Ala
 1045 1050 1055
 Ser Ile Phe Ser Leu Leu Trp Val Arg Ile Asp Pro Phe Leu Ala Lys
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cgccggcctc	gtcggtgtcg	gtggagtgtg	aatcggtgtg	tgttaggagga	178
atg gcg gcc aac aag	ggg atg gtg	gca ggc tct cac	aac cgc aac gag		226
Met Ala Asn Lys Gly	Met Val Ala	Gly Ser His	Asn Arg Asn Glu		
1	5	10	15		

ttc gtc atg atc	cgc cac gac	ggc gac gcg	cct gtc ccg	gct aag ccc	274
Phe Val Met Ile	Arg His Asp	Gly Asp Ala	Pro Val Pro	Ala Lys Pro	
20	25			30	

acg aag agt gcg aat	ggg cag gtc tgc	cag att tgt	ggc gac act	gtt	322
Thr Lys Ser Ala Asn	Gly Gln Val	Cys Gln Ile	Cys Gly Asp	Thr Val	
35	40		45		

ggc gtt tca gcc act	ggt gat gtc	ttt gtt gcc	tgc aat gag	tgt gcc	370
Gly Val Ser Ala Thr	Gly Asp Val	Phe Val Ala	Cys Asn Glu	Cys Ala	
50	55		60		

ttc cct gtc tgc cgc	cct tgc tat	gag tac gag	cgc aag gaa	ggg aac	418
Phe Pro Val Cys Arg	Pro Cys Tyr	Glu Tyr Glu	Arg Lys Glu	Gly Asn	
65	70		75	80	

caa tgc tgc cct cag	tgc aag act	aga tac aag	aga cag	aaa ggt	466
Gln Cys Cys Pro Gln	Cys Lys Thr	Arg Tyr Lys	Arg Gln	Lys Gly Ser	
85	90		95		

cct cga gtt cat	ggt gat gat	gag gag	gaa gat	gtt gat	514
Pro Arg Val His	Gly Asp Asp	Glu Glu	Asp Val	Asp Asp Leu	
100	105			110	

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aat gaa ttc aac tat aag caa ggc aat ggg aag ggc cca gag tgg cag Asn Glu Phe Asn Tyr Lys Gln Gly Asn Gly Lys Gly Pro Glu Trp Gln 115 120 125	562
ctt caa gga gat gac gct gat ctg tct tca tct gct cgc cat gac cca Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ser Ala Arg His Asp Pro 130 135 140	610
cac cat cgg att cca cgc ctt aca agt gga caa cag ata tct gga gag His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly Glu 145 150 155 160	658
atc cct gat gca tcc cct gac cgt cat tct atc cgc agt cca aca tcg Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr Ser 165 170 175	706
agc tat gtt gat cca agc gtt cca gtt cct gtg agg att gtg gac ccc Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp Pro 180 185 190	754
tcg aag gac ttg aat tcc tat ggg ctt aat agt gtt gac tgg aag gaa Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys Glu 195 200 205	802
aga gtt gag agc tgg agg gtt aaa cag gac aaa aat atg ttg caa gtg Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Leu Gln Val 210 215 220	850
act aat aaa tat cca gag gct aga gga gac atg gag ggg act ggc tca Thr Asn Lys Tyr Pro Glu Ala Arg Gly Asp Met Glu Gly Thr Gly Ser 225 230 235 240	898
aat gga gaa gat atg caa atg gtt gat gat gca cgc cta cct ttg agc Asn Gly Glu Asp Met Gln Met Val Asp Ala Arg Leu Pro Leu Ser 245 250 255	946
cgc att gtg cca att tcc tca aac cag ctc aac ctt tac cgg ata gta Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg Ile Val 260 265 270	994
atc att ctc cgt ctt atc atc ctg tgc ttc ttc ttc caa tat cgt atc Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe Phe Phe Gln Tyr Arg Ile 275 280 285	1042
agt cat cca gtg cgt aat gct tat gga ttg tgg cta gta tct gtt atc Ser His Pro Val Arg Asn Ala Tyr Gly Leu Trp Leu Val Ser Val Ile 290 295 300	1090
tgt gag gtc tgg ttt gcc ttg tcc tgg ctt cta gat cag ttc cca aaa Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe Pro Lys 305 310 315 320	1138
tgg tat cca atc aac cgt gag aca tat ctc gac agg ctt gca ttg agg Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu Arg 325 330 335	1186
tat gat aga gag gga gag cca tca cag ctg gct ccc att gat gtc ttt Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp Val Phe	1234

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340

345

350

gtc agt aca gtg gat cca ttg aag gaa cct cca ctg atc aca gcc aac Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr Ala Asn 355 360 365	1282
act gtt ttg tcc att ctt gct gtg gat tac cct gtt gac aaa gtg tca Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val Asp Lys Val Ser 370 375 380	1330
tgc tat gtt tct gat gat ggc tca gct atg ctg act ttt gag tct ctc Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu Ser Leu 385 390 395 400	1378
tct gaa act gcc gaa ttt gct aga aag tgg gtt ccc ttt tgt aag aag Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys Lys 405 410 415	1426
cac aat att gaa cca aga gct cca gaa ttt tac ttt gct caa aaa ata His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln Lys Ile 420 425 430	1474
gat tac ctg aag gac aaa att caa cct tca ttt gtt aag gaa aga cga Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu Arg Arg 435 440 445	1522
gca atg aag aga gag tat gaa gaa ttc aaa ata aga atc aat gcc ctt Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Ile Arg Ile Asn Ala Leu 450 455 460	1570
gtt gcc aaa gca cag aaa gtg cct gaa gag ggg tgg acc atg gct gat Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met Ala Asp 465 470 475 480	1618
gga act gct tgg cct ggg aat aac cct agg gac cat cct ggc atg att Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met Ile 485 490 495	1666
cag gtg ttc ttg ggg cac agt ggt ggg ctt gac act gat gga aat gaa Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn Glu 500 505 510	1714
tta cca cgt ctt gtc tat gtc tct cgt gaa aag aga cca ggc ttt cag Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe Gln 515 520 525	1762
cat cac aag aag gct ggt gca atg aat gca ctg att cgt gta tct gct His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser Ala 530 535 540	1810
gtg ctg aca aat ggt gcc tat ctt ctc aat gtg gat tgt gac cat tac Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His Tyr 545 550 555 560	1858
ttc aat agc agc aaa gct ctt aga gaa gca atg tgc ttc atg atg gat Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met Asp 565 570 575	1906

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cca gct cta gga agg aaa act tgt tat gta caa ttt cca caa aga ttt Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg Phe 580 585 590	1954
gat ggc att gac ttg cac gat cga tat gct aat agg aac ata gtc ttc Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val Phe 595 600 605	2002
ttt gat atc aac atg aaa ggt cta gat ggc att cag ggt cca gtc tat Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val Tyr 610 615 620	2050
gtg gga aca gga tgc tgt ttc aat agg cag gct ttg tat gga tat gat Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr Asp 625 630 635 640	2098
cct gtt ttg act gaa gct gat ctg gaa cct aac att gtt gtt aag agc Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Val Lys Ser 645 650 655	2146
tgc tgt ggt aga agg aag aga aag aac aag agt tat atg gat agt caa Cys Cys Gly Arg Arg Lys Arg Lys Asn Lys Ser Tyr Met Asp Ser Gln 660 665 670	2194
agc cgt att atg aag aga aca gaa tct tca gct ccc atc ttt aac atg Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn Met 675 680 685	2242
gaa gac atc gag gag ggt att gaa ggt tat gag gat gaa agg tca gtg Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser Val 690 695 700	2290
ctt atg tcc cag agg aaa ttg gag aaa cgc ttt ggt cag tct cca atc Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro Ile 705 710 715 720	2338
ttc att gca tcc acc ttt atg act caa ggt ggc ata cca cct tca aca Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser Thr 725 730 735	2386
aac cca gct tct cta ctg aag gaa gct atc cat gtt atc agc tgt ggg Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly 740 745 750	2434
tac gag gac aaa act gaa tgg gga aaa gag att ggc tgg atc tat ggt Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly 755 760 765	2482
tca gtt aca gag gat att ctg act ggg ttt aaa atg cat gca aga ggc Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg Gly 770 775 780	2530
tgg caa tca atc tac tgc atg cca cca cga cct tgt ttc aag ggt tct Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly Ser 785 790 795 800	2578
gca cca atc aat ctt tct gat cgt ctt aat cag gtg ctc cgt tgg gct Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp Ala	2626

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805	810	815	
ctt ggg tca gtg gaa att ctg ctt agc aga cat tgt cct ata tgg tat Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile Trp Tyr 820 825 830 835 840 845 850 855 860			2674 2722 2770 2818 2866 2914 2962 3010 3058 3106 3154 3202 3250 3298
ggc tac aat ggg cga ttg aag ctt ttg gag agg ctg gct tac att aac Gly Tyr Asn Gly Arg Leu Lys Leu Leu Glu Arg Leu Ala Tyr Ile Asn 835 840 845			
acc att gtt tat cca atc aca tct gtt ccg ctt atc gcc tat tgt gtg Thr Ile Val Tyr Pro Ile Thr Ser Val Pro Leu Ile Ala Tyr Cys Val 850 855 860			
ctt cct gct atc tgt ctt ctt acc aat aaa ttt atc att cct gag att Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu Ile 865 870 875 880			
agt aat tat gct gga atg ttc ttc att ctt ctt ttt gcc tcc att ttc Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile Phe 885 890 895			
gca act ggt ata ttg gag ctc aga tgg agt ggt gtt ggc att gaa gat Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu Asp 900 905 910			
tgg tgg aga aat gag cag ttt tgg gtt att ggt ggc acc tct gcc cat Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala His 915 920 925			
ctc ttc gcg gtg ttc cag ggt ctg ctg aaa gtg ttg gct ggg att gat Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile Asp 930 935 940			
acc aac ttc aca gtt acc tca aag gca tct gat gag gat ggc gac ttt Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp Phe 945 950 955 960			
gct gag cta tat gtg ttc aag tgg acc agt ttg ctc atc cct ccg acc Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro Thr 965 970 975			
act gtt ctt gtc att aac ctg gtc gga atg gtg gca gga att tcg tat Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser Tyr 980 985 990			
gcc att aac agc ggc tac caa tcc tgg ggt ccg ctc ttt gga aag ctg Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys Leu 995 1000 1005			
ttc ttc tcg atc tgg gtg atc ctc cat ctc tac ccc ttc ctc aag ggt Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys Gly 1010 1015 1020			
ctc atg ggc agg cag aac cgc acg cca aca atc gtc atc gtt tgg tcc Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser 1025 1030 1035 1040			

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atc ctc ctt gcg tct atc ttc tcc ttg ctg tgg gtg aag atc gat cct Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp Pro	3346
1045 1050 1055	

ttc atc tcc ccg aca cag aaa gct gcc gcc ttg ggg caa tgt ggt gtg Phe Ile Ser Pro Thr Gln Lys Ala Ala Leu Gly Gln Cys Gly Val	3394
1060 1065 1070	

aac t gctgatccag atttgactc ttatctgaag aggctcagcc aaagatctgc Asn	3448

ccccctcggt aaatacctga gggggctaga tggaaatttt ttgttgtaga tgaggatgga tctgcatcca agttatgcct ctgtttatta gcttctcggt gcccgggtgct gctgcagaca	3508
atcatggagc ctttctacct tgcttgtagt gctgccagc agcgtaaaatt gtgaattctg	3568
cattttttta tacgtggtgt ttattgtttt agagtaaattt atcatttttt tgaggtaact	3628
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	3725

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Thr Lys Ser Ala Asn Gly Gln Val Cys Gln Ile Cys Gly Asp Thr Val	
35 40 45	

Gly Val Ser Ala Thr Gly Asp Val Phe Val Ala Cys Asn Glu Cys Ala	
50 55 60	

Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Glu Gly Asn	
65 70 75 80	

Gln Cys Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Gln Lys Gly Ser	
85 90 95	

Pro Arg Val His Gly Asp Asp Glu Glu Asp Val Asp Asp Leu Asp	
100 105 110	

Asn Glu Phe Asn Tyr Lys Gln Gly Asn Gly Lys Gly Pro Glu Trp Gln	
115 120 125	

Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ser Ala Arg His Asp Pro	
130 135 140	

His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly Glu	
145 150 155 160	

Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr Ser	
165 170 175	

Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp Pro	
180 185 190	

Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys Glu	
195 200 205	

Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Leu Gln Val	
210 215 220	

Thr Asn Lys Tyr Pro Glu Ala Arg Gly Asp Met Glu Gly Thr Gly Ser	
225 230 235 240	

Asn Gly Glu Asp Met Gln Met Val Asp Asp Ala Arg Leu Pro Leu Ser	
245 250 255	

Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg Ile Val	
260 265 270	

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Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe Phe Phe Gln Tyr Arg Ile
 275 280 285
 Ser His Pro Val Arg Asn Ala Tyr Gly Leu Trp Leu Val Ser Val Ile
 290 295 300
 Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe Pro Lys
 305 310 315 320
 Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu Arg
 325 330 335
 Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp Val Phe
 340 345 350
 Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr Ala Asn
 355 360 365
 Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val Asp Lys Val Ser
 370 375 380
 Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu Ser Leu
 385 390 395 400
 Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys Lys
 405 410 415
 His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln Lys Ile
 420 425 430
 Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu Arg Arg
 435 440 445
 Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Ile Arg Ile Asn Ala Leu
 450 455 460
 Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met Ala Asp
 465 470 475 480
 Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met Ile
 485 490 495
 Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn Glu
 500 505 510
 Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe Gln
 515 520 525
 His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser Ala
 530 535 540
 Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His Tyr
 545 550 555 560
 Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met Asp
 565 570 575
 Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg Phe
 580 585 590
 Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val Phe
 595 600 605
 Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val Tyr
 610 615 620
 Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr Asp
 625 630 635 640
 Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Val Lys Ser
 645 650 655
 Cys Cys Gly Arg Arg Lys Arg Lys Asn Lys Ser Tyr Met Asp Ser Gln
 660 665 670
 Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn Met
 675 680 685
 Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser Val
 690 695 700
 Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro Ile
 705 710 715 720
 Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser Thr
 725 730 735

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Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly
 740 745 750
 Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly
 755 760 765
 Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg Gly
 770 775 780
 Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly Ser
 785 790 795 800
 Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp Ala
 805 810 815
 Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile Trp Tyr
 820 825 830
 Gly Tyr Asn Gly Arg Leu Lys Leu Leu Glu Arg Leu Ala Tyr Ile Asn
 835 840 845
 Thr Ile Val Tyr Pro Ile Thr Ser Val Pro Leu Ile Ala Tyr Cys Val
 850 855 860
 Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu Ile
 865 870 875 880
 Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile Phe
 885 890 895
 Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu Asp
 900 905 910
 Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala His
 915 920 925
 Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile Asp
 930 935 940
 Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp Phe
 945 950 955 960
 Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro Thr
 965 970 975
 Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser Tyr
 980 985 990
 Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys Leu
 995 1000 1005
 Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys Gly
 1010 1015 1020
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 1025 1030 1035 1040
 Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp Pro
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 Asn Cys

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 Met Glu Ala Ser Ala Gly Leu
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gtg gcc ggc tcg cat aac cgg aac gag ctg gtg gtg atc cgc cgc gac 283
 Val Ala Gly Ser His Asn Arg Asn Glu Leu Val Val Ile Arg Arg Asp
 10 15 20

cgc gag tcg gga gcc gcg ggc ggc gcg cgc cgg gcg gag gcg 331
 Arg Glu Ser Gly Ala Ala Gly Gly Ala Ala Arg Arg Ala Glu Ala
 25 30 35

ccg tgc cag ata tgc ggc gac gag gtc ggg gtg ggc ttc gac ggg gag 379
 Pro Cys Gln Ile Cys Gly Asp Glu Val Gly Val Gly Phe Asp Gly Glu
 40 45 50 55

ccc ttc gtg gcg tgc aac gag tgc gcc ttc ccc gtc tgc cgc gcc tgc 427
 Pro Phe Val Ala Cys Asn Glu Cys Ala Phe Pro Val Cys Arg Ala Cys
 60 65 70

tac gag tac gag cgc cgc gag ggc tcg caa gcg tgc ccc cag tgc agg 475
 Tyr Glu Tyr Glu Arg Arg Glu Gly Ser Gln Ala Cys Pro Gln Cys Arg
 75 80 85

acc cgc tac aag cgc ctc aag ggc tgc ccc cgg gtg gcc ggc gac gag 523
 Thr Arg Tyr Lys Arg Leu Lys Gly Cys Pro Arg Val Ala Gly Asp Glu
 90 95 100

gag gag gac ggc gtc gac gac ctg gag ggc gag ttc ggc ctg cag gac 571
 Glu Glu Asp Gly Val Asp Asp Leu Glu Gly Glu Phe Gly Leu Gln Asp
 105 110 115

ggc gcc gcc cac gag gac gac ccc cag tac gtc gcc gag tcc atg ctc 619
 Gly Ala Ala His Glu Asp Asp Pro Gln Tyr Val Ala Glu Ser Met Leu
 120 125 130 135

agg gcg cag atg agc tac ggc cgc ggc gac gac ccc ggc ttc 667
 Arg Ala Gln Met Ser Tyr Gly Arg Gly Asp Ala His Pro Gly Phe
 140 145 150

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Ser Pro Val Pro Asn Val Pro Leu Leu Thr Asn Gly Gln Met Val Asp		
155	160	165
 gac atc ccg ccg gag cag cac gcg ctc gtg ccg tcc tac atg agc ggc		
Asp Ile Pro Pro Glu Gln His Ala Leu Val Pro Ser Tyr Met Ser Gly		
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185	190	195
 aac ctt cca gtg caa ccg aga tcc atg gac ccg tcc aag gat ctg gcc		
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 gcc tac gga tat ggc agc gtg gcc tgg aag gag aga atg gag ggc tgg		
Ala Tyr Gly Tyr Gly Ser Val Ala Trp Lys Glu Arg Met Glu Gly Trp		
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Lys Gln Lys Gln Glu Arg Leu Gln His Val Arg Ser Glu Gly Gly		
235	240	245
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Asp Trp Asp Gly Asp Ala Asp Leu Pro Leu Met Asp Glu Ala Arg		
250	255	260
260		
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Gln Pro Leu Ser Arg Lys Val Pro Ile Ser Ser Arg Ile Asn Pro		
265	270	275
 tac agg atg att atc gtt atc ccg ttg gtg gtt ttg ggt ttc ttc ttc		
Tyr Arg Met Ile Ile Val Ile Arg Leu Val Val Leu Gly Phe Phe Phe		
280	285	290
295		
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His Tyr Arg Val Met His Pro Ala Lys Asp Ala Phe Ala Leu Trp Leu		
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Ile Ser Val Ile Cys Glu Ile Trp Phe Ala Met Ser Trp Ile Leu Asp		
315	320	325
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Gln Phe Pro Lys Trp Leu Pro Ile Glu Arg Glu Thr Tyr Leu Asp Arg		
330	335	340
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Leu Ser Leu Arg Phe Asp Lys Glu Gly Gln Pro Ser Gln Leu Ala Pro		
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Ile Asp Phe Phe Val Ser Thr Val Asp Pro Thr Lys Glu Pro Pro Leu		
360	365	370
375		
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Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr Pro Val		
380		
 1387		

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380

385

390

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ttc agc aaa aag ttt aat atc gag cct cgt gct cct gag tgg tac ttc Phe Ser Lys Lys Phe Asn Ile Glu Pro Arg Ala Pro Glu Trp Tyr Phe 425 430 435	1531
caa cag aag ata gac tac ctg aaa gac aag gtt gct gct tca ttt gtt Gln Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val Ala Ala Ser Phe Val 440 445 450 455	1579
agg gag agg agg gcg atg aag aga gaa tac gag gaa ttc aag gta agg Arg Glu Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg 460 465 470	1627
atc aat gcc ttg gtt gca aaa gcc caa aag gtt cct gag gaa gga tgg Ile Asn Ala Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp 475 480 485	1675
aca atg caa gat gga agc ccc tgg cct gga aac aac gta cgc gat cat Thr Met Gln Asp Gly Ser Pro Trp Pro Gly Asn Asn Val Arg Asp His 490 495 500	1723
cct gga atg att cag gta ttc ctt ggc caa agt ggc ggt cgt gat gtg Pro Gly Met Ile Gln Val Phe Leu Gly Gln Ser Gly Gly Arg Asp Val 505 510 515	1771
gaa gga aat gag ttg cct cgc ctg gtt tat gtc tcg aga gaa aag agg Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg 520 525 530 535	1819
cca ggt tat aac cat cac aag aag gct ggt gcc atg aat gca ctg gtc Pro Gly Tyr Asn His His Lys Lys Ala Gly Ala Met Asn Ala Leu Val 540 545 550	1867
cgt gtc tct gct gtc tta tca aat gct gca tac cta ttg aac ttg gac Arg Val Ser Ala Val Leu Ser Asn Ala Ala Tyr Leu Leu Asn Leu Asp 555 560 565	1915
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ttc atg atg gat cct ttg gtg ggg aag aaa gtg tgc tat gta cag ttc Phe Met Met Asp Pro Leu Val Gly Lys Lys Val Cys Tyr Val Gln Phe 585 590 595	2011
cct cag agg ttt gat ggt att gac aaa aat gat cga tac gct aac agg Pro Gln Arg Phe Asp Gly Ile Asp Lys Asn Asp Arg Tyr Ala Asn Arg 600 605 610 615	2059

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aac gtt gtc ttt ttt gac atc aac atg aaa ggt ttg gac ggt att caa Asn Val Val Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln 620 625 630	2107
gga ccc att tat gtg ggt act gga tgt gtt ttc aga cgg cag gca ctg Gly Pro Ile Tyr Val Gly Thr Gly Cys Val Phe Arg Arg Gln Ala Leu 635 640 645	2155
tat ggt tat gat gct cct aaa acg aag aag cca cca tca aga act tgc Tyr Gly Tyr Asp Ala Pro Lys Thr Lys Lys Pro Pro Ser Arg Thr Cys 650 655 660	2203
aac tgc tgg ccc aag tgg tgc ctc tct tgc tgc agc agg aac aag Asn Cys Trp Pro Lys Trp Cys Leu Ser Cys Cys Ser Arg Asn Lys 665 670 675	2251
aat aaa aag aag act aca aaa cca aag acg gag aag aag aaa aga tta Asn Lys Lys Lys Thr Thr Lys Pro Lys Thr Glu Lys Lys Lys Arg Leu 680 685 690 695	2299
ttt ttc aag aaa gca gaa aac cca tct cct gca tat gct ttg ggt gaa Phe Phe Lys Lys Ala Glu Asn Pro Ser Pro Ala Tyr Ala Leu Gly Glu 700 705 710	2347
att gat gaa ggt gct cca ggt gct gat atc gag aag gcc gga atc gta Ile Asp Glu Gly Ala Pro Gly Ala Asp Ile Glu Lys Ala Gly Ile Val 715 720 725	2395
aatcaa cag aaa cta gag aag aaa ttt ggg cag tct tct gtt ttt gtc Asn Gln Gln Lys Leu Glu Lys Lys Phe Gly Gln Ser Ser Val Phe Val 730 735 740	2443
gca tca aca ctt ctt gag aac gga ggg acc ctg aag agc gca agt cca Ala Ser Thr Leu Leu Glu Asn Gly Gly Thr Leu Lys Ser Ala Ser Pro 745 750 755	2491
gct tct ctt ctg aag gaa gct ata cat gtt atc agc tgc ggc tac gaa Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly Tyr Glu 760 765 770 775	2539
gac aag acc gac tgg gga aaa gag att ggc tgg att tac gga tcg atc Asp Lys Thr Asp Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly Ser Ile 780 785 790	2587
aca gag gat atc ttg act gga ttt aag atg cac tgc cat ggc tgg cgg Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Cys His Gly Trp Arg 795 800 805	2635
tct att tac tgc atc ccg aag cgg cct gca ttc aaa ggt tct gcg cct Ser Ile Tyr Cys Ile Pro Lys Arg Pro Ala Phe Lys Gly Ser Ala Pro 810 815 820	2683
ctg aac ctt tcc gac cgt ctt cac cag gtc ctt cgc tgg gcc ctt ggg Leu Asn Leu Ser Asp Arg Leu His Gln Val Leu Arg Trp Ala Leu Gly 825 830 835	2731
tcc gtc gaa att ttc ttc agc aag cac tgc cca ctt tgg tac gga tac Ser Val Glu Ile Phe Phe Ser Lys His Cys Pro Leu Trp Tyr Gly Tyr	2779

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840	845	850	855	
ggc ggc ggg cta aaa ttc ctg gaa agg ttt tct tat atc aac tcc atc Gly Gly Gly Leu Lys Phe Leu Glu Arg Phe Ser Tyr Ile Asn Ser Ile 860 865 870				2827
gtt tat ccc tgg acg tcc att cct ctc ctg gct tac tgt acc ttg cct Val Tyr Pro Trp Thr Ser Ile Pro Leu Leu Ala Tyr Cys Thr Leu Pro 875 880 885				2875
gcc atc tgc ctg ctc acg ggg aag ttt atc aca cca gag ctt acc aat Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile Thr Pro Glu Leu Thr Asn 890 895 900				2923
gtc gcc agt atc tgg ttc atg gca ctt ttc atc tgc atc tcc gtg acc Val Ala Ser Ile Trp Phe Met Ala Leu Phe Ile Cys Ile Ser Val Thr 905 910 915				2971
ggc atc ctg gaa atg agg tgg agt ggc gtg gcc atc gac gac tgg tgg Gly Ile Leu Glu Met Arg Trp Ser Gly Val Ala Ile Asp Asp Trp Trp 920 925 930 935				3019
agg aac gag cag ttc tgg gtc atc gga ggc gtt tcg gcg cat ctg ttc Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Val Ser Ala His Leu Phe 940 945 950				3067
gcg gtg ttc cag ggc ctg ctg aag gtg ttc gcc ggc atc gac acg agc Ala Val Phe Gln Gly Leu Leu Lys Val Phe Ala Gly Ile Asp Thr Ser 955 960 965				3115
ttc acc gtg acg tcg aag gcc ggg gac gac gag gag ttc tcg gag ctg Phe Thr Val Thr Ser Lys Ala Gly Asp Asp Glu Phe Ser Glu Leu 970 975 980				3163
tac acg ttc aag tgg acc acc ctg ctg ata ccc ccg acc acg ctc ctc Tyr Thr Phe Lys Trp Thr Thr Leu Leu Ile Pro Pro Thr Thr Leu Leu 985 990 995				3211
ctg ctg aac ttc atc ggg gtg gtg gcc ggg atc tcg aac gcg atc aac Leu Leu Asn Phe Ile Gly Val Val Ala Gly Ile Ser Asn Ala Ile Asn 1000 1005 1010 1015				3259
aac ggg tac gag tcg tgg ggc ccc ctg ttc ggg aag ctc ttc ttc gcc Asn Gly Tyr Glu Ser Trp Gly Pro Leu Phe Gly Lys Leu Phe Ala 1020 1025 1030				3307
ttc tgg gtg atc gtc cac ctg tac ccg ttc ctc aag ggt ctg gtg ggg Phe Trp Val Ile Val His Leu Tyr Pro Phe Leu Lys Gly Leu Val Gly 1035 1040 1045				3355
agg cag aac agg acg ccg acg atc gtc atc gtc tgg tcc atc ctg ctg Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser Ile Leu Leu 1050 1055 1060				3403
gcc tcg atc ttc tcg ctc ctg tgg gtc cgc gtc gac ccg ttc ctc gcc Ala Ser Ile Phe Ser Leu Leu Trp Val Arg Val Asp Pro Phe Leu Ala 1065 1070 1075				3451

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aag agc aac ggc ccg ctc ctg gag gag tgt ggc ctg gac tgc a	3494
Lys Ser Asn Gly Pro Leu Leu Glu Glu Cys Gly Leu Asp Cys	
1080 1085 1090	

actgaagtgg gggccccctg tcactcgaag ttctgtcacg ggcaattac gcctgat	3554
tttgttggat ttgttgttggaa attctttgtct gtagatagaa accacatgtc cacgcac	3614
ctgctgtgtc cattggagca ggagagagg gcctgtgtct gtttgttagaa taaaat	3674
gttttaaagt tatacagtga tgcacatcc agtgcagg gtattccctt tttacagtct	3734
gtatatttagc gacaaaggac atattggta ggagttgtat tctttgtaa aaaaaaaaaa	3794
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Leu	Val	Val	Ile	Arg	Arg	Asp	Arg	Glu	Ser	Gly	Ala	Ala	Gly	Gly	Gly	
			20					25						30		
Ala	Ala	Arg	Arg	Ala	Glu	Ala	Pro	Cys	Gln	Ile	Cys	Gly	Asp	Glu	Val	
			35				40				45					
Gly	Val	Gly	Phe	Asp	Gly	Glu	Pro	Phe	Val	Ala	Cys	Asn	Glu	Cys	Ala	
			50			55				60						
Phe	Pro	Val	Cys	Arg	Ala	Cys	Tyr	Glu	Tyr	Glu	Arg	Arg	Glu	Gly	Ser	
			65			70			75				80			
Gln	Ala	Cys	Pro	Gln	Cys	Arg	Thr	Arg	Tyr	Lys	Arg	Leu	Lys	Gly	Cys	
						85			90				95			
Pro	Arg	Val	Ala	Gly	Asp	Glu	Glu	Asp	Gly	Val	Asp	Asp	Leu	Glu		
			100			105				110						
Gly	Glu	Phe	Gly	Leu	Gln	Asp	Gly	Ala	Ala	His	Glu	Asp	Asp	Pro	Gln	
			115			120				125						
Tyr	Val	Ala	Glu	Ser	Met	Leu	Arg	Ala	Gln	Met	Ser	Tyr	Gly	Arg	Gly	
			130			135				140						
Gly	Asp	Ala	His	Pro	Gly	Phe	Ser	Pro	Val	Pro	Asn	Val	Pro	Leu	Leu	
			145			150			155				160			
Thr	Asn	Gly	Gln	Met	Val	Asp	Asp	Ile	Pro	Pro	Glu	Gln	His	Ala	Leu	
						165			170				175			
Val	Pro	Ser	Tyr	Met	Ser	Gly	Gly	Gly	Gly	Gly	Lys	Arg	Ile	His		
			180			185				190						
Pro	Leu	Pro	Phe	Ala	Asp	Pro	Asn	Leu	Pro	Val	Gln	Pro	Arg	Ser	Met	
			195			200				205						
Asp	Pro	Ser	Lys	Asp	Leu	Ala	Ala	Tyr	Gly	Tyr	Ser	Val	Ala	Trp		
			210			215				220						
Lys	Glu	Arg	Met	Glu	Gly	Trp	Lys	Gln	Lys	Gln	Glu	Arg	Leu	Gln	His	
			225			230			235				240			
Val	Arg	Ser	Glu	Gly	Gly	Asp	Trp	Asp	Gly	Asp	Asp	Ala	Asp	Leu		
			245			250				255						
Pro	Leu	Met	Asp	Glu	Ala	Arg	Gln	Pro	Leu	Ser	Arg	Lys	Val	Pro	Ile	
			260			265				270						
Ser	Ser	Ser	Arg	Ile	Asn	Pro	Tyr	Arg	Met	Ile	Ile	Val	Ile	Arg	Leu	
			275			280				285						
Val	Val	Leu	Gly	Phe	Phe	His	Tyr	Arg	Val	Met	His	Pro	Ala	Lys		
			290			295				300						
Asp	Ala	Phe	Ala	Leu	Trp	Leu	Ile	Ser	Val	Ile	Cys	Glu	Ile	Trp	Phe	
			305			310			315				320			
Ala	Met	Ser	Trp	Ile	Leu	Asp	Gln	Phe	Pro	Lys	Trp	Leu	Pro	Ile	Glu	

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325	330	335
Arg Glu Thr Tyr Leu Asp Arg Leu Ser Leu Arg Phe Asp Lys Glu Gly		
340	345	350
Gln Pro Ser Gln Leu Ala Pro Ile Asp Phe Phe Val Ser Thr Val Asp		
355	360	365
Pro Thr Lys Glu Pro Pro Leu Val Thr Ala Asn Thr Val Leu Ser Ile		
370	375	380
Leu Ser Val Asp Tyr Pro Val Glu Lys Val Ser Cys Tyr Val Ser Asp		
385	390	395
Asp Gly Ala Ala Met Leu Thr Phe Glu Ala Leu Ser Glu Thr Ser Glu		
405	410	415
Phe Ala Lys Lys Trp Val Pro Phe Ser Lys Lys Phe Asn Ile Glu Pro		
420	425	430
Arg Ala Pro Glu Trp Tyr Phe Gln Gln Lys Ile Asp Tyr Leu Lys Asp		
435	440	445
Lys Val Ala Ala Ser Phe Val Arg Glu Arg Arg Ala Met Lys Arg Glu		
450	455	460
Tyr Glu Glu Phe Lys Val Arg Ile Asn Ala Leu Val Ala Lys Ala Gln		
465	470	475
Lys Val Pro Glu Glu Gly Trp Thr Met Gln Asp Gly Ser Pro Trp Pro		
485	490	495
Gly Asn Asn Val Arg Asp His Pro Gly Met Ile Gln Val Phe Leu Gly		
500	505	510
Gln Ser Gly Gly Arg Asp Val Glu Gly Asn Glu Leu Pro Arg Leu Val		
515	520	525
Tyr Val Ser Arg Glu Lys Arg Pro Gly Tyr Asn His His Lys Lys Ala		
530	535	540
Gly Ala Met Asn Ala Leu Val Arg Val Ser Ala Val Leu Ser Asn Ala		
545	550	555
Ala Tyr Leu Leu Asn Leu Asp Cys Asp His Tyr Ile Asn Asn Ser Lys		
565	570	575
Ala Ile Lys Glu Ala Met Cys Phe Met Met Asp Pro Leu Val Gly Lys		
580	585	590
Lys Val Cys Tyr Val Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Lys		
595	600	605
Asn Asp Arg Tyr Ala Asn Arg Asn Val Val Phe Phe Asp Ile Asn Met		
610	615	620
Lys Gly Leu Asp Gly Ile Gln Gly Pro Ile Tyr Val Gly Thr Gly Cys		
625	630	635
Val Phe Arg Arg Gln Ala Leu Tyr Gly Tyr Asp Ala Pro Lys Thr Lys		
645	650	655
Lys Pro Pro Ser Arg Thr Cys Asn Cys Trp Pro Lys Trp Cys Leu Ser		
660	665	670
Cys Cys Cys Ser Arg Asn Lys Asn Lys Lys Lys Thr Thr Lys Pro Lys		
675	680	685
Thr Glu Lys Lys Arg Leu Phe Phe Lys Lys Ala Glu Asn Pro Ser		
690	695	700
Pro Ala Tyr Ala Leu Gly Glu Ile Asp Glu Gly Ala Pro Gly Ala Asp		
705	710	715
Ile Glu Lys Ala Gly Ile Val Asn Gln Gln Lys Leu Glu Lys Lys Phe		
725	730	735
Gly Gln Ser Ser Val Phe Val Ala Ser Thr Leu Leu Glu Asn Gly Gly		
740	745	750
Thr Leu Lys Ser Ala Ser Pro Ala Ser Leu Leu Lys Glu Ala Ile His		
755	760	765
Val Ile Ser Cys Gly Tyr Glu Asp Lys Thr Asp Trp Gly Lys Glu Ile		
770	775	780
Gly Trp Ile Tyr Gly Ser Ile Thr Glu Asp Ile Leu Thr Gly Phe Lys		

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785	790	795	800
Met His Cys His Gly Trp Arg Ser Ile Tyr Cys Ile Pro Lys Arg Pro			
805	810	815	
Ala Phe Lys Gly Ser Ala Pro Leu Asn Leu Ser Asp Arg Leu His Gln			
820	825	830	
Val Leu Arg Trp Ala Leu Gly Ser Val Glu Ile Phe Phe Ser Lys His			
835	840	845	
Cys Pro Leu Trp Tyr Gly Tyr Gly Gly Leu Lys Phe Leu Glu Arg			
850	855	860	
Phe Ser Tyr Ile Asn Ser Ile Val Tyr Pro Trp Thr Ser Ile Pro Leu			
865	870	875	880
Leu Ala Tyr Cys Thr Leu Pro Ala Ile Cys Leu Leu Thr Gly Lys Phe			
885	890	895	
Ile Thr Pro Glu Leu Thr Asn Val Ala Ser Ile Trp Phe Met Ala Leu			
900	905	910	
Phe Ile Cys Ile Ser Val Thr Gly Ile Leu Glu Met Arg Trp Ser Gly			
915	920	925	
Val Ala Ile Asp Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly			
930	935	940	
Gly Val Ser Ala His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val			
945	950	955	960
Phe Ala Gly Ile Asp Thr Ser Phe Thr Val Thr Ser Lys Ala Gly Asp			
965	970	975	
Asp Glu Glu Phe Ser Glu Leu Tyr Thr Phe Lys Trp Thr Thr Leu Leu			
980	985	990	
Ile Pro Pro Thr Thr Leu Leu Leu Asn Phe Ile Gly Val Val Ala			
995	1000	1005	
Gly Ile Ser Asn Ala Ile Asn Asn Gly Tyr Glu Ser Trp Gly Pro Leu			
1010	1015	1020	
Phe Gly Lys Leu Phe Phe Ala Phe Trp Val Ile Val His Leu Tyr Pro			
1025	1030	1035	1040
Phe Leu Lys Gly Leu Val Gly Arg Gln Asn Arg Thr Pro Thr Ile Val			
1045	1050	1055	
Ile Val Trp Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val			
1060	1065	1070	
Arg Val Asp Pro Phe Leu Ala Lys Ser Asn Gly Pro Leu Leu Glu Glu			
1075	1080	1085	
Cys Gly Leu Asp Cys Asn			
1090			

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25

<210> 28
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<400> 28
tcagttgcag tccaggccac actcc
25

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<210> 29
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gtccctttct ctcgtccctc ctccccccgt atatgttaa cccggcccgct tactactact	180
actagcagca gcagcgctct cgccaggaa gatccgggtt tgatccgtgc cccgctcgga	240
tctcgggact ggtgccggct ctgcccaggc cccaggctcc aggccagctc cctcgacgtt	300
tctcggcgag ctcgcttgcc atg gag ggc gac gcg gac ggc gtg aag tcg ggg	353
Met Glu Gly Asp Ala Asp Gly Val Lys Ser Gly	
1 5 10	

agg cgc ggt ggc gga cag gtg tgc cag atc tgc ggc gac ggc gtg ggc	401
Arg Arg Gly Gly Gln Val Cys Gln Ile Cys Gly Asp Gly Val Gly	
15 20 25	

acc acg gcg gag ggg gac gtc ttc gcc gcc tgc gac gtc tgc ggg ttt	449
Thr Thr Ala Glu Gly Asp Val Phe Ala Ala Cys Asp Val Cys Gly Phe	
30 35 40	

ccg gtg tgc cgc ccc tgc tac gag tac gag cgc aag gac ggc acg cag	497
Pro Val Cys Arg Pro Cys Tyr Glu Arg Lys Asp Gly Thr Gln	
45 50 55	

gcg tgc ccc cag tgc aag acc aag tac aag cgc cac aag ggg agc ccg	545
Ala Cys Pro Gln Cys Lys Thr Lys Tyr Lys Arg His Lys Gly Ser Pro	
60 65 70 75	

gcg atc cgt ggg gag gaa gga gac gac act gat gcc gat agc gac ttc	593
Ala Ile Arg Gly Glu Gly Asp Asp Thr Asp Ala Asp Ser Asp Phe	
80 85 90	

aat tac ctt gca tct ggc aat gag gac cag aag cag aat gcc gac	641
Asn Tyr Leu Ala Ser Gly Asn Glu Asp Gln Lys Gln Ile Ala Asp	
95 100 105	

aga atg cgc agc tgg cgc atg aac gtt ggg ggc agc ggg gat gtt ggt	689
Arg Met Arg Ser Trp Arg Met Asn Val Gly Gly Ser Gly Asp Val Gly	
110 115 120	

cgc ccc aag tat gac agt ggc gag atc ggg ctt acc aag tat gac agt	737
Arg Pro Lys Tyr Asp Ser Gly Glu Ile Gly Leu Thr Lys Tyr Asp Ser	
125 130 135	

ggc gag att cct cgg gga tac atc cca tca gtc act aac agc cag atc	785
Gly Glu Ile Pro Arg Gly Tyr Ile Pro Ser Val Thr Asn Ser Gln Ile	
140 145 150 155	

tca gga gaa atc cct ggt gct tcc cct gac cat cat atg atg tcc cca	833
Ser Gly Glu Ile Pro Gly Ala Ser Pro Asp His His Met Met Ser Pro	
160 165 170	

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act ggg aac att ggc aag cgt gct cca ttt ccc tat gtg aac cat tcg		881
Thr Gly Asn Ile Gly Lys Arg Ala Pro Phe Pro Tyr Val Asn His Ser		
175	180	185
cca aat ccg tca agg gag ttc tct ggt agc att ggg aat gtt gcc tgg		929
Pro Asn Pro Ser Arg Glu Phe Ser Gly Ser Ile Gly Asn Val Ala Trp		
190	195	200
aaa gag agg gtt gat ggc tgg aaa atg aag cag gac aag ggg acg att		977
Lys Glu Arg Val Asp Gly Trp Lys Met Lys Gln Asp Lys Gly Thr Ile		
205	210	215
ccc atg acg aat ggc aca agc att gct ccc tct gag ggt cgg ggt gtt		1025
Pro Met Thr Asn Gly Thr Ser Ile Ala Pro Ser Glu Gly Arg Gly Val		
220	225	230
235		
ggt gat att gat gca tca act gat tac aac atg gaa gat gcc tta ttg		1073
Gly Asp Ile Asp Ala Ser Thr Asp Tyr Asn Met Glu Asp Ala Leu Leu		
240	245	250
aac gac gaa act cga cag cct cta tct agg aaa gtt cca ctt cct tcc		1121
Asn Asp Glu Thr Arg Gln Pro Leu Ser Arg Lys Val Pro Leu Pro Ser		
255	260	265
tcc agg ata aat cca tac agg atg gtc att gtg ctg cga ttg att gtt		1169
Ser Arg Ile Asn Pro Tyr Arg Met Val Ile Val Leu Arg Leu Ile Val		
270	275	280
cta agc atc ttc ttg cac tac cgt atc aca aat cct gtg cgc aat gca		1217
Leu Ser Ile Phe Leu His Tyr Arg Ile Thr Asn Pro Val Arg Asn Ala		
285	290	295
tac cca tta tgg ctt cta tct gtt ata tgt gag atc tgg ttt gct ctt		1265
Tyr Pro Leu Trp Leu Leu Ser Val Ile Cys Glu Ile Trp Phe Ala Leu		
300	305	310
315		
tcg tgg ata ttg gat cag ttc cct aag tgg ttt cca atc aac cgg gag		1313
Ser Trp Ile Leu Asp Gln Phe Pro Lys Trp Phe Pro Ile Asn Arg Glu		
320	325	330
acg tac ctt gat agg ctg gca tta agg tat gac cgg gaa ggt gag cca		1361
Thr Tyr Leu Asp Arg Leu Ala Leu Arg Tyr Asp Arg Glu Gly Glu Pro		
335	340	345
tct cag ttg gct gtt gac att ttc gtc agt aca gtc gac cca atg		1409
Ser Gln Leu Ala Ala Val Asp Ile Phe Val Ser Thr Val Asp Pro Met		
350	355	360
aag gag cct cct ctt gtc act gcc aat acc gtg cta tcc att ctt gct		1457
Lys Glu Pro Pro Leu Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ala		
365	370	375
gtg gat tac cct gtg gat aag gtc tct tgc tat gta tct gat gat gga		1505
Val Asp Tyr Pro Val Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly		
380	385	390
395		
gct gcg atg ctg aca ttt gat gca cta gct gag act tca gag ttt gct		1553

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Ala Ala Met Leu Thr Phe Asp Ala Leu Ala Glu Thr Ser Glu Phe Ala			
400	405	410	
aga aaa tgg gta cca ttt gtt aag aag tac aac att gaa cct aga gct			1601
Arg Lys Trp Val Pro Phe Val Lys Lys Tyr Asn Ile Glu Pro Arg Ala			
415	420	425	
cct gaa tgg tac ttc tcc cag aaa att gat tac ttg aag gac aaa gtg			1649
Pro Glu Trp Tyr Phe Ser Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val			
430	435	440	
cac cct tca ttt gtt aaa gac cgc cgg gcc atg aag aga gaa tat gaa			1697
His Pro Ser Phe Val Lys Asp Arg Arg Ala Met Lys Arg Glu Tyr Glu			
445	450	455	
gaa ttc aaa gtt agg gta aat ggc ctt gtt gct aag gca cag aaa gtt			1745
Glu Phe Lys Val Arg Val Asn Gly Leu Val Ala Lys Ala Gln Lys Val			
460	465	470	475
cct gag gaa gga tgg atc atg caa gat ggc aca cca tgg cca gga aac			1793
Pro Glu Glu Gly Trp Ile Met Gln Asp Gly Thr Pro Trp Pro Gly Asn			
480	485	490	
aat acc mgg gac cat cct gga atg att cag gtt ttc ctt ggt cac agt			1841
Asn Thr Xaa Asp His Pro Gly Met Ile Gln Val Phe Leu Gly His Ser			
495	500	505	
ggt ggc ctt gat act gag ggc aat gag cta ccc cgt ttg gtc tat gtt			1889
Gly Gly Leu Asp Thr Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val			
510	515	520	
tct cgt gaa aag cgt cct gga ttc cag cat cac aag aaa gct ggt gcc			1937
Ser Arg Glu Lys Arg Pro Gly Phe Gln His His Lys Lys Ala Gly Ala			
525	530	535	
atg aat gct ctt gtt cgt gtc tca gct gtg ctt acc aat gga caa tac			1985
Met Asn Ala Leu Val Arg Val Ser Ala Val Leu Thr Asn Gly Gln Tyr			
540	545	550	555
atg ttg aat ctt gat tgt gat cac tac att aac aac agt aag gct ctc			2033
Met Leu Asn Leu Asp Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Leu			
560	565	570	
agg gaa gct atg tgc ttc ctt atg gac cct aac cta gga agg agt gtc			2081
Arg Glu Ala Met Cys Phe Leu Met Asp Pro Asn Leu Gly Arg Ser Val			
575	580	585	
tgc tac gtc cag ttt ccc cag aga ttc gat att gac agg aat gat			2129
Cys Tyr Val Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Arg Asn Asp			
590	595	600	
cga tat gcc aac agg aac acc gtg ttt ttc gat att aac ttg aga ggt			2177
Arg Tyr Ala Asn Arg Asn Thr Val Phe Phe Asp Ile Asn Leu Arg Gly			
605	610	615	
ctt gat ggc atc caa gga cca gtt tat gtc gga act ggc tgt gtt ttc			2225
Leu Asp Gly Ile Gln Gly Pro Val Tyr Val Gly Thr Gly Cys Val Phe			
620	625	630	635

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aac cga aca gct cta tat ggt tat gag ccc cca att aag cag aag aag Asn Arg Thr Ala Leu Tyr Gly Tyr Glu Pro Pro Ile Lys Gln Lys Lys 640 645 650	2273
ggt ggt ttc ttg tca tca cta tgt ggc ggt agg aag aag gca agc aaa Gly Gly Phe Leu Ser Ser Leu Cys Gly Gly Arg Lys Lys Ala Ser Lys 655 660 665	2321
tca aag aag ggc tcg gac aag aag tcg cag aag cat gtg gac agt Ser Lys Lys Gly Ser Asp Lys Lys Ser Gln Lys His Val Asp Ser 670 675 680	2369
tct gtg cca gta ttc aac ctt gaa gat ata gag gag gga gtt gaa ggc Ser Val Pro Val Phe Asn Leu Glu Asp Ile Glu Glu Gly Val Glu Gly 685 690 695	2417
gct gga ttt gac gac gag aaa tca ctt ctt atg tct caa atg agc ctg Ala Gly Phe Asp Asp Glu Lys Ser Leu Leu Met Ser Gln Met Ser Leu 700 705 710 715	2465
gag aag aga ttt ggc cag tcc gca gcg ttt gtt gcc tcc act ctg atg Glu Lys Arg Phe Gly Gln Ser Ala Ala Phe Val Ala Ser Thr Leu Met 720 725 730	2513
gag tat ggt ggt gtt cct cag tcc gca act ccg gag tct ctt ctg aaa Glu Tyr Gly Val Pro Gln Ser Ala Thr Pro Glu Ser Leu Leu Lys 735 740 745	2561
gaa gct atc cat gtt ata agc tgt ggc tat gag gac aag act gaa tgg Glu Ala Ile His Val Ile Ser Cys Gly Tyr Glu Asp Lys Thr Glu Trp 750 755 760	2609
gga act gag atc ggg tgg atc tac ggt tct gtg aca gaa gac att ctc Gly Thr Glu Ile Gly Trp Ile Tyr Gly Ser Val Thr Glu Asp Ile Leu 765 770 775	2657
acc gga ttc aag atg cac gcg cga ggc tgg cgg tcg atc tac tgc atg Thr Gly Phe Lys Met His Ala Arg Gly Trp Arg Ser Ile Tyr Cys Met 780 785 790 795	2705
ccc aag cgg cca gct ttc aag ggg tct gcc ccc atc aat ctt tcg gac Pro Lys Arg Pro Ala Phe Lys Gly Ser Ala Pro Ile Asn Leu Ser Asp 800 805 810	2753
cgt ctg aac cag gtg ctc cgg tgg gct ctt ggg tcc gtg gag atc ctc Arg Leu Asn Gln Val Leu Arg Trp Ala Leu Gly Ser Val Glu Ile Leu 815 820 825	2801
ttc agc cgg cac tgc ccc ctg tgg tac ggc tac gga ggg cgg ctc aag Phe Ser Arg His Cys Pro Leu Trp Tyr Gly Tyr Gly Arg Leu Lys 830 835 840	2849
ttc ctg gag aga ttc gcg tac atc aac acc acc atc tac ccg ctc acg Phe Leu Glu Arg Phe Ala Tyr Ile Asn Thr Thr Ile Tyr Pro Leu Thr 845 850 855	2897
tcc atc ccg ctt ctc atc tac tgc atc ctg ccc gcc atc tgt ctg ctc	2945

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Ser Ile Pro Leu Leu Ile Tyr Cys Ile Leu Pro Ala Ile Cys Leu Leu 860 865 870 875	
acc gga aag ttc atc att cca gag atc agc aac ttc gcc agc atc tgg Thr Gly Lys Phe Ile Ile Pro Glu Ile Ser Asn Phe Ala Ser Ile Trp 880 885 890	2993
ttc atc tcc ctc ttc atc tcg atc ttc gcc acg ggc atc ctg gag atg Phe Ile Ser Leu Phe Ile Ser Ile Phe Ala Thr Gly Ile Leu Glu Met 895 900 905	3041
agg tgg agc ggg gtg ggc atc gac gag tgg tgg agg aac gag cag ttc Arg Trp Ser Gly Val Gly Ile Asp Glu Trp Trp Arg Asn Glu Gln Phe 910 915 920	3089
tgg gtg atc ggg ggc atc tcc gcg cac ctc ttc gcc gtg ttc cag ggc Trp Val Ile Gly Gly Ile Ser Ala His Leu Phe Ala Val Phe Gln Gly 925 930 935	3137
ctg ctc aag gtg ctg gcc ggc atc gac acc aac ttc acc gtc acc tcc Leu Leu Lys Val Leu Ala Gly Ile Asp Thr Asn Phe Thr Val Thr Ser 940 945 950 955	3185
aag gcc tcg gac gag gac ggc gac ttc gcg gag ctg tac atg ttc aag Lys Ala Ser Asp Glu Asp Gly Asp Phe Ala Glu Leu Tyr Met Phe Lys 960 965 970	3233
tgg acg acg ctc ctg atc ccg ccc acc acc atc ctg atc atc aac ctg Trp Thr Thr Leu Leu Ile Pro Pro Thr Thr Ile Leu Ile Ile Asn Leu 975 980 985	3281
gtc ggc gtc gtc gcc ggc atc tcc tac gcc atc aac agc gga tac cag Val Gly Val Ala Gly Ile Ser Tyr Ala Ile Asn Ser Gly Tyr Gln 990 995 1000	3329
tcg tgg ggc ccg ctc ttc ggc aag ctc ttc ttc gcc ttc tgg gtc atc Ser Trp Gly Pro Leu Phe Gly Lys Leu Phe Phe Ala Phe Trp Val Ile 1005 1010 1015	3377
gtc cac ctg tac ccg ctc aag ggc ctc atg ggc agg cag aac cgc Val His Leu Tyr Pro Phe Leu Lys Gly Leu Met Gly Arg Gln Asn Arg 1020 1025 1030 1035	3425
acc ccg acc atc gtc gtc tgg gcc atc ctg ctg gcg tcc atc ttc Thr Pro Thr Ile Val Val Trp Ala Ile Leu Leu Ala Ser Ile Phe 1040 1045 1050	3473
tcc ttg ctg tgg gtt cgc atc gac ccc ttc acc acc cgc gtc act ggc Ser Leu Leu Trp Val Arg Ile Asp Pro Phe Thr Thr Arg Val Thr Gly 1055 1060 1065	3521
ccg gat acc cag acg tgt ggc atc aac t gctaggaaag tggaaggttt Pro Asp Thr Gln Thr Cys Gly Ile Asn 1070 1075	3569
gtactttgtta gaaacggagg aataccacgt gccatctgtt gtctgttaag ttatatatat ataaggcagca agtggcgta tttacagcta cgtacagacc agtggatatt gttaccaca aagttttact tgtgttaata tgcattctt tggatata aaaaaaaaaaaaaaaa 1080 1085 1090	3629 3689 3746

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<210> 30
<211> 1077
<212> PRT
<213> Zea mays

<400> 30

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1 5 10 15
Gln Val Cys Gln Ile Cys Gly Asp Gly Val Gly Thr Thr Ala Glu Gly
20 25 30
Asp Val Phe Ala Ala Cys Asp Val Cys Gly Phe Pro Val Cys Arg Pro
35 40 45
Cys Tyr Glu Tyr Glu Arg Lys Asp Gly Thr Gln Ala Cys Pro Gln Cys
50 55 60
Lys Thr Lys Tyr Lys Arg His Lys Gly Ser Pro Ala Ile Arg Gly Glu
65 70 75 80
Glu Gly Asp Asp Thr Asp Ala Asp Ser Asp Phe Asn Tyr Leu Ala Ser
85 90 95
Gly Asn Glu Asp Gln Lys Gln Lys Ile Ala Asp Arg Met Arg Ser Trp
100 105 110
Arg Met Asn Val Gly Gly Ser Gly Asp Val Gly Arg Pro Lys Tyr Asp
115 120 125
Ser Gly Glu Ile Gly Leu Thr Lys Tyr Asp Ser Gly Glu Ile Pro Arg
130 135 140
Gly Tyr Ile Pro Ser Val Thr Asn Ser Gln Ile Ser Gly Glu Ile Pro
145 150 155 160
Gly Ala Ser Pro Asp His His Met Met Ser Pro Thr Gly Asn Ile Gly
165 170 175
Lys Arg Ala Pro Phe Pro Tyr Val Asn His Ser Pro Asn Pro Ser Arg
180 185 190
Glu Phe Ser Gly Ser Ile Gly Asn Val Ala Trp Lys Glu Arg Val Asp
195 200 205
Gly Trp Lys Met Lys Gln Asp Lys Gly Thr Ile Pro Met Thr Asn Gly
210 215 220
Thr Ser Ile Ala Pro Ser Glu Gly Arg Gly Val Gly Asp Ile Asp Ala
225 230 235 240
Ser Thr Asp Tyr Asn Met Glu Asp Ala Leu Leu Asn Asp Glu Thr Arg
245 250 255
Gln Pro Leu Ser Arg Lys Val Pro Leu Pro Ser Ser Arg Ile Asn Pro
260 265 270
Tyr Arg Met Val Ile Val Leu Arg Leu Ile Val Leu Ser Ile Phe Leu
275 280 285
His Tyr Arg Ile Thr Asn Pro Val Arg Asn Ala Tyr Pro Leu Trp Leu
290 295 300
Leu Ser Val Ile Cys Glu Ile Trp Phe Ala Leu Ser Trp Ile Leu Asp
305 310 315 320
Gln Phe Pro Lys Trp Phe Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg
325 330 335
Leu Ala Leu Arg Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Ala
340 345 350
Val Asp Ile Phe Val Ser Thr Val Asp Pro Met Lys Glu Pro Pro Leu
355 360 365
Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val
370 375 380
Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ala Ala Met Leu Thr
385 390 395 400
Phe Asp Ala Leu Ala Glu Thr Ser Glu Phe Ala Arg Lys Trp Val Pro

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Phe	Val	Lys	Lys	Tyr	Asn	Ile	Glu	Pro	Arg	Ala	Pro	Glu	Trp	Tyr	Phe
405															415
420								425						430	
Ser	Gln	Lys	Ile	Asp	Tyr	Leu	Lys	Asp	Lys	Val	His	Pro	Ser	Phe	Val
435								440						445	
Lys	Asp	Arg	Arg	Ala	Met	Lys	Arg	Glu	Tyr	Glu	Glu	Phe	Lys	Val	Arg
450						455						460			
Val	Asn	Gly	Leu	Val	Ala	Lys	Ala	Gln	Lys	Val	Pro	Glu	Glu	Gly	Trp
465						470				475					480
Ile	Met	Gln	Asp	Gly	Thr	Pro	Trp	Pro	Gly	Asn	Asn	Thr	Xaa	Asp	His
485						490									495
Pro	Gly	Met	Ile	Gln	Val	Phe	Leu	Gly	His	Ser	Gly	Gly	Leu	Asp	Thr
500						505				510					
Glu	Gly	Asn	Glu	Leu	Pro	Arg	Leu	Val	Tyr	Val	Ser	Arg	Glu	Lys	Arg
515						520							525		
Pro	Gly	Phe	Gln	His	His	Lys	Lys	Ala	Gly	Ala	Met	Asn	Ala	Leu	Val
530						535				540					
Arg	Val	Ser	Ala	Val	Leu	Thr	Asn	Gly	Gln	Tyr	Met	Leu	Asn	Leu	Asp
545						550				555					560
Cys	Asp	His	Tyr	Ile	Asn	Asn	Ser	Lys	Ala	Leu	Arg	Glu	Ala	Met	Cys
565						570							575		
Phe	Leu	Met	Asp	Pro	Asn	Leu	Gly	Arg	Ser	Val	Cys	Tyr	Val	Gln	Phe
580						585							590		
Pro	Gln	Arg	Phe	Asp	Gly	Ile	Asp	Arg	Asn	Asp	Arg	Tyr	Ala	Asn	Arg
595						600							605		
Asn	Thr	Val	Phe	Phe	Asp	Ile	Asn	Leu	Arg	Gly	Leu	Asp	Gly	Ile	Gln
610						615				620					
Gly	Pro	Val	Tyr	Val	Gly	Thr	Gly	Cys	Val	Phe	Asn	Arg	Thr	Ala	Leu
625						630				635					640
Tyr	Gly	Tyr	Glu	Pro	Pro	Ile	Lys	Gln	Lys	Lys	Gly	Gly	Phe	Leu	Ser
645						650				655					
Ser	Leu	Cys	Gly	Arg	Lys	Lys	Ala	Ser	Lys	Ser	Lys	Lys	Gly	Ser	
660						665				670					
Asp	Lys	Lys	Ser	Gln	Lys	His	Val	Asp	Ser	Ser	Val	Pro	Val	Phe	
675						680				685					
Asn	Leu	Glu	Asp	Ile	Glu	Glu	Gly	Val	Glu	Gly	Ala	Gly	Phe	Asp	Asp
690						695				700					
Glu	Lys	Ser	Leu	Leu	Met	Ser	Gln	Met	Ser	Leu	Glu	Lys	Arg	Phe	Gly
705						710				715					720
Gln	Ser	Ala	Ala	Phe	Val	Ala	Ser	Thr	Leu	Met	Glu	Tyr	Gly	Gly	Val
725						730				735					
Pro	Gln	Ser	Ala	Thr	Pro	Glu	Ser	Leu	Leu	Lys	Glu	Ala	Ile	His	Val
740						745				750					
Ile	Ser	Cys	Gly	Tyr	Glu	Asp	Lys	Thr	Glu	Trp	Gly	Thr	Glu	Ile	Gly
755						760				765					
Trp	Ile	Tyr	Gly	Ser	Val	Thr	Glu	Asp	Ile	Leu	Thr	Gly	Phe	Lys	Met
770						775				780					
His	Ala	Arg	Gly	Trp	Arg	Ser	Ile	Tyr	Cys	Met	Pro	Lys	Arg	Pro	Ala
785						790				795					800
Phe	Lys	Gly	Ser	Ala	Pro	Ile	Asn	Leu	Ser	Asp	Arg	Leu	Asn	Gln	Val
805						810								815	
Leu	Arg	Trp	Ala	Leu	Gly	Ser	Val	Glu	Ile	Leu	Phe	Ser	Arg	His	Cys
820						825				830					
Pro	Leu	Trp	Tyr	Gly	Tyr	Gly	Gly	Arg	Leu	Lys	Phe	Leu	Glu	Arg	Phe
835						840				845					
Ala	Tyr	Ile	Asn	Thr	Thr	Ile	Tyr	Pro	Leu	Thr	Ser	Ile	Pro	Leu	Leu
850						855				860					
Ile	Tyr	Cys	Ile	Leu	Pro	Ala	Ile	Cys	Leu	Leu	Thr	Gly	Lys	Phe	Ile

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865	870	875	880
Ile Pro Glu Ile Ser Asn Phe Ala Ser Ile Trp Phe Ile Ser Leu Phe			
885	890	895	
Ile Ser Ile Phe Ala Thr Gly Ile Leu Glu Met Arg Trp Ser Gly Val			
900	905	910	
Gly Ile Asp Glu Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly			
915	920	925	
Ile Ser Ala His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu			
930	935	940	
Ala Gly Ile Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu			
945	950	955	960
Asp Gly Asp Phe Ala Glu Leu Tyr Met Phe Lys Trp Thr Thr Leu Leu			
965	970	975	
Ile Pro Pro Thr Thr Ile Leu Ile Ile Asn Leu Val Gly Val Val Ala			
980	985	990	
Gly Ile Ser Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu			
995	1000	1005	
Phe Gly Lys Leu Phe Phe Ala Phe Trp Val Ile Val His Leu Tyr Pro			
1010	1015	1020	
Phe Leu Lys Gly Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val			
1025	1030	1035	1040
Val Val Trp Ala Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val			
1045	1050	1055	
Arg Ile Asp Pro Phe Thr Thr Arg Val Thr Gly Pro Asp Thr Gln Thr			
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Cys Gly Ile Asn Cys			
1075			

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25

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25

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ggtcgccaac gccgctcgga tctagaggcc cgcacggcc gatttgtctc cgccccctc

60

120

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gtcgggtttg gtgtcggtgg cgtgtggagc cgctcggtg ggaggcagccgg ggagggagcg	180
gag atg gcg gcc aac aag ggg atg gtg gcg ggc tcg cac aac cgc aac	228
Met Ala Ala Asn Lys Gly Met Val Ala Gly Ser His Asn Arg Asn	
1 5 10 15	
gag ttc gtc atg atc cgc cac gac ggc gat gtg ccg ggc tcg gct aag	276
Glu Phe Val Met Ile Arg His Asp Gly Asp Val Pro Gly Ser Ala Lys	
20 25 30	
ccc aca aag agt gcg aat gga cag gtc tgc cag att tgc ggt gac tct	324
Pro Thr Lys Ser Ala Asn Gly Gln Val Cys Gln Ile Cys Gly Asp Ser	
35 40 45	
gtg ggt gtt tca gcc act ggt gat gtc ttt gtt gcc tgc aat gag tgt	372
Val Gly Val Ser Ala Thr Gly Asp Val Phe Val Ala Cys Asn Glu Cys	
50 55 60	
gcc ttc cct gtc tgc cgc cca tgc tat gag tat gag cgc aag gag ggg	420
Ala Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Glu Gly	
65 70 75	
aac caa tgc tgc ccc cag tgc aag act aga tac aag aga cag aaa ggt	468
Asn Gln Cys Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Gln Lys Gly	
80 85 90 95	
agc cct cga gtt cat ggt gat gag gat gag gaa gat gtt gat gac cta	516
Ser Pro Arg Val His Gly Asp Glu Asp Glu Asp Val Asp Asp Leu	
100 105 110	
gac aat gaa ttc aac tac aag caa ggc agt ggg aaa ggc cca gag tgg	564
Asp Asn Glu Phe Asn Tyr Lys Gln Gly Ser Gly Lys Gly Pro Glu Trp	
115 120 125	
caa ctg caa gga gat gat gct gat ctg tct tca tct gct cgc cat gag	612
Gln Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ser Ala Arg His Glu	
130 135 140	
cca cat cat cgg att cca cgc ctg aca agc ggt caa cag ata tct gga	660
Pro His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly	
145 150 155	
gag att cct gat gct tcc cct gac cgt cat tct atc cgc agt cca aca	708
Glu Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr	
160 165 170 175	
tcg agc tat gtt gat cca agc gtc cca gtt cct gtg agg att gtg gac	756
Ser Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp	
180 185 190	
ccc tcg aag gac ttg aat tcc tat ggg ctt aat agt gtt gac tgg aag	804
Pro Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys	
195 200 205	
gaa aga gtt gag agc tgg agg gtt aaa cag gac aaa aat atg atg caa	852
Glu Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Met Gln	
210 215 220	
gtg act aat aaa tat cca gag gct aga gga gga gac atg gag ggg act	900

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Val Thr Asn Lys Tyr Pro Glu Ala Arg Gly Gly Asp Met Glu Gly Thr			
225	230	235	
ggc tca aat gga gaa nat atg caa atg gtt gat gat gca cgg cta cct			948
Gly Ser Asn Gly Glu Xaa Met Gln Met Val Asp Asp Ala Arg Leu Pro			
240	245	250	255
ttg agc cgt atc gtg cca att tcc tca aac cag ctc aac ctt tac cgg			996
Leu Ser Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg			
260	265	270	
gta gtg atc att ctc cgt ctt atc atc ctg tgc ttc ttc ttc cag tat			1044
Val Val Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe Phe Gln Tyr			
275	280	285	
cgt gtc agt cat cca gtg cgt gat gct tat gga tta tgg cta gta tct			1092
Arg Val Ser His Pro Val Arg Asp Ala Tyr Gly Leu Trp Leu Val Ser			
290	295	300	
gtt atc tgc gag gtc tgg ttt gcc ttg tct tgg ctt cta gat cag ttc			1140
Val Ile Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe			
305	310	315	
cca aaa tgg tat cca atc aac cgt gag aca tat ctt gac agg ctt gca			1188
Pro Lys Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala			
320	325	330	335
ttg agg tat gat aga gag gga gag cca tca cag ctg gct ccc att gat			1236
Leu Arg Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp			
340	345	350	
gtc ttc gtc agt aca gtg gat cca ttg aag gaa cct cca ctg atc aca			1284
Val Phe Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr			
355	360	365	
gcc aac act gtt tcc att ctt tct gtg gat tac cct gtt gac aaa			1332
Ala Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr Pro Val Asp Lys			
370	375	380	
gtg tca tgc tat gtt tct gat gat ggt tca gct atg ctg act ttt gag			1380
Val Ser Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu			
385	390	395	
tct ctc tca gaa acc gca gaa ttt gct aga aag tgg gtt ccc ttt tgt			1428
Ser Leu Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys			
400	405	410	415
aag aag cac aat att gaa cca aga gct cca gaa ttt tac ttt gct caa			1476
Lys Lys His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln			
420	425	430	
aaa ata gat tac ctg aag gac aaa att caa cct tca ttt gtt aag gaa			1524
Lys Ile Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu			
435	440	445	
aga cgc gca atg aag agg gag tat gaa gaa ttc aaa gta aga atc aat			1572
Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg Ile Asn			
450	455	460	

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gcc ctt gtt gcc aaa gca cag aaa gtg cct gaa gag ggg tgg acc atg Ala Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met 465 470 475	1620
gct gat gga act gca tgg cct ggg aat aat cct agg gac cat cct ggc Ala Asp Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly 480 485 490 495	1668
atg att cag gtt ttc ttg ggg cac agt ggt ggg ctc gac act gat gga Met Ile Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly 500 505 510	1716
aat gag tta cca cgt ctt gtc tat gtc tct cgt gaa aag aga cca ggc Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly 515 520 525	1764
ttt cag cat cac aag aag gct ggt gca atg aat gcg ctg att cgt gta Phe Gln His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val 530 535 540	1812
tct gct gtg ctg aca aat ggt gcc tat ctt ctc aat gtg gat tgc gac Ser Ala Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp 545 550 555	1860
cat tac ttc aat agc agc aaa gct ctt aga gaa gca atg tgc ttc atg His Tyr Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met 560 565 570 575	1908
atg gat ccg gct cta gga agg aaa act tgt tat gta caa ttt cca cag Met Asp Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln 580 585 590	1956
aga ttt gat ggc att gac ttg cac gat cga tat gct aat cgg aac ata Arg Phe Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile 595 600 605	2004
gtt ttc ttt gat atc aac atg aaa ggt ctg gat ggc att cag ggt cca Val Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro 610 615 620	2052
gtt tac gtg gga aca gga tgc tgt ttc aat aga cag gct ttg tat gga Val Tyr Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly 625 630 635	2100
tac gat cct gtt ttg act gaa gct gat ctg gag cca aac att gtt att Tyr Asp Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Ile 640 645 650 655	2148
aag agc tgc tgt ggt aga agg aag aaa aag aac aag agt tat atg gat Lys Ser Cys Cys Gly Arg Arg Lys Lys Lys Asn Lys Ser Tyr Met Asp 660 665 670	2196
agt caa agc cgt att atg aag aga aca gaa tct tca gct ccc atc ttc Ser Gln Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe 675 680 685	2244
aat atg gaa gac atc gaa gag ggt att gaa ggt tac gag gat gaa agg	2292

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Asn Met Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg		
690	695	700
tca gtg ctt atg tcc cag agg aaa ttg gag aaa cgc ttt ggt cag tct		2340
Ser Val Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser		
705	710	715
cct att ttc att gca tcc acc ttt atg aca caa ggt ggc ata cca cct		2388
Pro Ile Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro		
720	725	730
tca aca aac cca gct tct cta cta aag gaa gct atc cat gtc atc agt		2436
Ser Thr Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser		
740	745	750
tgt gga tat gag gac aaa act gaa tgg gga aaa gag att ggc tgg atc		2484
Cys Gly Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile		
755	760	765
tat ggt tca gta acg gag gat att ctg act ggg ttt aaa atg cat gca		2532
Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala		
770	775	780
agg ggc tgg caa tca atc tac tgc atg cca cca cga cct tgt ttc aag		2580
Arg Gly Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys		
785	790	795
ggt tct gca cca atc aat ctt tcc gat cgt ctt aat cag gtg ctc cgt		2628
Gly Ser Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg		
800	805	810
tgg gct ctt ggg tca gtg gaa att ctg ctt agt aga cat tgt cct atc		2676
Trp Ala Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile		
820	825	830
tgg tat ggt tac aat gga cga ttg aag ctt ttg gag agg ctg gct tac		2724
Trp Tyr Gly Tyr Asn Gly Arg Leu Lys Leu Leu Glu Arg Leu Ala Tyr		
835	840	845
atc aac act att gta tat cca atc aca tcc att ccg ctt att gcc tat		2772
Ile Asn Thr Ile Val Tyr Pro Ile Thr Ser Ile Pro Leu Ile Ala Tyr		
850	855	860
tgt gtg ctt ccc gct atc tgc ctc ctt acc aat aaa ttt atc att cct		2820
Cys Val Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro		
865	870	875
gag att agc aat tat gct ggg atg ttc ttc att ctt ctt ttc gcc tcc		2868
Glu Ile Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser		
880	885	890
att ttt gcc act ggt ata ttg gag ctt aga tgg agt ggt gtt ggc att		2916
Ile Phe Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile		
900	905	910
gaa gat tgg tgg aga aat gag cag ttt tgg gtt att ggt ggc acc tct		2964
Glu Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser		
915	920	925

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gcc cat ctc ttc gca gtg ttc cag ggt ctg ctg aaa gtt ttg gct ggg Ala His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly	930	935	940	3012
att gat acc aac ttc aca gtt acc tca aag gca tct gat gag gat ggc Ile Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly	945	950	955	3060
gac ttt gct gag cta tat gtg ttc aag tgg acc agt ttg ctc att cct Asp Phe Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro	960	965	970	3108
ccg acc act gtt ctt gtc att aac ctg gtc gga atg gtg gca gga att Pro Thr Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile	980	985	990	3156
tct tat gcc att aac agt ggc tac caa tcc tgg ggt ccg ctc ttt gga Ser Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly	995	1000	1005	3204
aag ctg ttc ttc tcg atc tgg gtg atc ctc cat ctc tac ccc ttc ctc Lys Leu Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu	1010	1015	1020	3252
aag ggt ctc atg gga agg cag aac cgc aca cca aca atc gtc att gtc Lys Gly Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val	1025	1030	1035	3300
tgg tcc atc ctt ctt gca tct atc ttc tcc ttg ctg tgg gtg aag atc Trp Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile	1040	1045	1050	3348
gat cct ttc atc tcc ccg aca cag aaa gct gct gcc ttg ggg caa tgt Asp Pro Phe Ile Ser Pro Thr Gln Lys Ala Ala Leu Gly Gln Cys	1060	1065	1070	3396
ggc gtc aac t gctgatcgag acagtgactc ttatggaaaggctcaatc Gly Val Asn				3446
aagatctgcc ccctcggtata aatacctgag gaggcttagat gggatttcct tttgttgttag gtgaggatgg atttgcattct aagttatgcc tctgttcatt agttttcccttgcgggtgc tgctgcgcac taagaatcac ggagccttc taccttccat gtacgcgcag ccagcagcgt aagatgtgaa ttttgaagtt ttgttatgcg tgcatgttat tgtttttagag taaaattatca tttgtttgtg ggaactgttc acacgagctt ataatggcaa tgctgttatt taaaaaaaaa aaaaaaaa				3506
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Met Ala Ala Asn Lys Gly Met Val Ala Gly Ser His Asn Arg Asn Glu 1 5 10 15				
Phe Val Met Ile Arg His Asp Gly Asp Val Pro Gly Ser Ala Lys Pro 20 25 30				

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 35 40 45
 Gly Val Ser Ala Thr Gly Asp Val Phe Val Ala Cys Asn Glu Cys Ala
 50 55 60
 Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Glu Gly Asn
 65 70 75 80
 Gln Cys Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Gln Lys Gly Ser
 85 90 95
 Pro Arg Val His Gly Asp Glu Asp Glu Asp Val Asp Asp Leu Asp
 100 105 110
 Asn Glu Phe Asn Tyr Lys Gln Gly Ser Gly Lys Gly Pro Glu Trp Gln
 115 120 125
 Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ser Ala Arg His Glu Pro
 130 135 140
 His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly Glu
 145 150 155 160
 Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr Ser
 165 170 175
 Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp Pro
 180 185 190
 Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys Glu
 195 200 205
 Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Met Gln Val
 210 215 220
 Thr Asn Lys Tyr Pro Glu Ala Arg Gly Gly Asp Met Glu Gly Thr Gly
 225 230 235 240
 Ser Asn Gly Glu Xaa Met Gln Met Val Asp Asp Ala Arg Leu Pro Leu
 245 250 255
 Ser Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg Val
 260 265 270
 Val Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe Phe Phe Gln Tyr Arg
 275 280 285
 Val Ser His Pro Val Arg Asp Ala Tyr Gly Leu Trp Leu Val Ser Val
 290 295 300
 Ile Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe Pro
 305 310 315 320
 Lys Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu
 325 330 335
 Arg Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp Val
 340 345 350
 Phe Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr Ala
 355 360 365
 Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr Pro Val Asp Lys Val
 370 375 380
 Ser Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu Ser
 385 390 395 400
 Leu Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys
 405 410 415
 Lys His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln Lys
 420 425 430
 Ile Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu Arg
 435 440 445
 Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg Ile Asn Ala
 450 455 460
 Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met Ala
 465 470 475 480
 Asp Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met
 485 490 495

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Ile Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn
 500 505 510
 Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe
 515 520 525
 Gln His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser
 530 535 540
 Ala Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His
 545 550 555 560
 Tyr Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met
 565 570 575
 Asp Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg
 580 585 590
 Phe Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val
 595 600 605
 Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val
 610 615 620
 Tyr Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr
 625 630 635 640
 Asp Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Ile Lys
 645 650 655
 Ser Cys Cys Gly Arg Arg Lys Lys Asn Lys Ser Tyr Met Asp Ser
 660 665 670
 Gln Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn
 675 680 685
 Met Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser
 690 695 700
 Val Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro
 705 710 715 720
 Ile Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser
 725 730 735
 Thr Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys
 740 745 750
 Gly Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr
 755 760 765
 Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg
 770 775 780
 Gly Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly
 785 790 795 800
 Ser Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp
 805 810 815
 Ala Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile Trp
 820 825 830
 Tyr Gly Tyr Asn Gly Arg Leu Lys Leu Leu Glu Arg Leu Ala Tyr Ile
 835 840 845
 Asn Thr Ile Val Tyr Pro Ile Thr Ser Ile Pro Leu Ile Ala Tyr Cys
 850 855 860
 Val Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu
 865 870 875 880
 Ile Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile
 885 890 895
 Phe Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu
 900 905 910
 Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala
 915 920 925
 His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile
 930 935 940
 Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp
 945 950 955 960

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Phe Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro
 965 970 975
 Thr Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser
 980 985 990
 Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys
 995 1000 1005
 Leu Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys
 1010 1015 1020
 Gly Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp
 1025 1030 1035 1040
 Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp
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 Val Asn Cys
 1075

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gcggaaagtgg aggggaggaa gcg atg gag gcg agc gcc ggg ctg gtg gcc ggc 173
Met Glu Ala Ser Ala Gly Leu Val Ala Gly
1 5 10

tcc cac aac cgc aac gag ctc gtc atc cgc cgc gac ggc gat ccc 221
Ser His Asn Arg Asn Glu Leu Val Val Ile Arg Arg Asp Gly Asp Pro
15 20 25

ggg ccg aag ccg ccg cgg gag cag aac ggg cag gtg tgc cag att tgc 269
Gly Pro Lys Pro Pro Arg Glu Gln Asn Gly Gln Val Cys Gln Ile Cys
30 35 40

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ggc gac gac gtc ggc ctt gcc ccc ggc ggg gac ccc ttc gtg gcg tgc Gly Asp Asp Val Gly Leu Ala Pro Gly Gly Asp Pro Phe Val Ala Cys	45	50	55	317
aac gag tgc gcc ttc ccc gtc tgc cgg gac tgc tac gaa tac gag cgc Asn Glu Cys Ala Phe Pro Val Cys Arg Asp Cys Tyr Glu Tyr Glu Arg	60	65	70	365
cg ^g gag ggc acg cag aac tgc ccc cag tgc aag act cga tac aag cgc Arg Glu Gly Thr Gln Asn Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg	75	80	85	413
ctc aag ggc tgc caa cgt gtg acc ggt gac gag gag gag gac ggc gtc Leu Lys Gly Cys Gln Arg Val Thr Gly Asp Glu Glu Glu Asp Gly Val	95	100	105	461
gat gac ctg gac aac gag ttc aac tgg gac ggc cat gac tgc cag tct Asp Asp Leu Asp Asn Glu Phe Asn Trp Asp Gly His Asp Ser Gln Ser	110	115	120	509
gtg gcc gag tcc atg ctc tac ggc cac atg agc tac ggc cgt gga ggt Val Ala Glu Ser Met Leu Tyr Gly His Met Ser Tyr Gly Arg Gly Gly	125	130	135	557
gac cct aat ggc gcg cca caa gct ttc cag ctc aac ccc aat gtt cca Asp Pro Asn Gly Ala Pro Gln Ala Phe Gln Leu Asn Pro Asn Val Pro	140	145	150	605
ctc ctc acc aac ggg caa atg gtg gat gac atc cca ccg gag cag cac Leu Leu Thr Asn Gly Gln Met Val Asp Asp Ile Pro Pro Glu Gln His	155	160	165	653
gc ^g ctg gtg cct tct ttc atg ggt ggt ggg gga aag agg ata cat ccc Ala Leu Val Pro Ser Phe Met Gly Gly Gly Lys Arg Ile His Pro	175	180	185	701
ctt cct tat gc ^g gat ccc agc tta cct gtg caa ccc agg tct atg gac Leu Pro Tyr Ala Asp Pro Ser Leu Pro Val Gln Pro Arg Ser Met Asp	190	195	200	749
cca tcc aag gat ctt gct gca tat ggg tat ggt agt gtt gct tgg aag Pro Ser Lys Asp Leu Ala Ala Tyr Gly Tyr Gly Ser Val Ala Trp Lys	205	210	215	797
gaa cgg atg gag aat tgg aag cag aga caa gag agg atg cac cag acg Glu Arg Met Glu Asn Trp Lys Gln Arg Gln Glu Arg Met His Gln Thr	220	225	230	845
ggg aat gat ggt ggt gat gat ggt gac gat gct gat cta cca cta Gly Asn Asp Gly Gly Asp Asp Gly Asp Asp Ala Asp Leu Pro Leu	235	240	245	893
atg gat gaa gca aga caa ctt tcc agg aaa att cca ctt cca tca Met Asp Glu Ala Arg Gln Gln Leu Ser Arg Lys Ile Pro Leu Pro Ser	255	260	265	941
agc cag att aat cca tat agg atg att atc att att cgg ctt gtg gtt				989

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Ser Gln Ile Asn Pro Tyr Arg Met Ile Ile Ile Arg Leu Val Val				
270	275	280		
ttg ggg ttc ttc cac tac cga gtg atg cat ccg gtg aat gat gca				1037
Leu Gly Phe Phe His Tyr Arg Val Met His Pro Val Asn Asp Ala				
285	290	295		
ttt gct ttg tgg ctc ata tct gtt atc tgt gaa atc tgg ttt gcc atg				1085
Phe Ala Leu Trp Leu Ile Ser Val Ile Cys Glu Ile Trp Phe Ala Met				
300	305	310		
tct tgg att ctt gatcaa ttc cca aag tgg ttc cct att gag aga gag				1133
Ser Trp Ile Leu Asp Gln Phe Pro Lys Trp Phe Pro Ile Glu Arg Glu				
315	320	325	330	
act tac cta gac cggtc tca ctg agg ttc gac aag gaa ggc cag cca				1181
Thr Tyr Leu Asp Arg Leu Ser Leu Arg Phe Asp Lys Glu Gly Gln Pro				
335	340	345		
tct caa ctt gct cca att gat ttc ttt gtc agt acg gtt gat ccc tta				1229
Ser Gln Leu Ala Pro Ile Asp Phe Phe Val Ser Thr Val Asp Pro Leu				
350	355	360		
aag gaa cct cct ttg gtc aca aca aat act gtt cta tct atc ctt tcg				1277
Lys Glu Pro Pro Leu Val Thr Thr Asn Thr Val Leu Ser Ile Leu Ser				
365	370	375		
gtg gat tat cct gtt gat aag gtt tct tgc tat gtt tct gat gat ggt				1325
Val Asp Tyr Pro Val Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly				
380	385	390		
gct gca atg cta acg ttt gaa gca tta tct gaa aca tct gaa ttt gca				1373
Ala Ala Met Leu Thr Phe Glu Ala Leu Ser Glu Thr Ser Glu Phe Ala				
395	400	405	410	
aag aaa tgg gtt cct ttc tgc aaa cgg tac aat att gaa cct cgc gct				1421
Lys Lys Trp Val Pro Phe Cys Lys Arg Tyr Asn Ile Glu Pro Arg Ala				
415	420	425		
cca gag tgg tac ttc caa cag aag ata gac tac ttg aaa gac aag gtg				1469
Pro Glu Trp Tyr Phe Gln Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val				
430	435	440		
gca gca aac ttt gtt agg gag agg aga gca atg aag aga gag tat gag				1517
Ala Ala Asn Phe Val Arg Glu Arg Arg Ala Met Lys Arg Glu Tyr Glu				
445	450	455		
gaa ttc aag gtg aga atc aat gcc tta gtt gcc aaa gcc cag aaa gtt				1565
Glu Phe Lys Val Arg Ile Asn Ala Leu Val Ala Lys Ala Gln Lys Val				
460	465	470		
cct gaa gaa gga tgg aca atg caa gat gga acc ccc tgg cct gga aac				1613
Pro Glu Glu Gly Trp Thr Met Gln Asp Gly Thr Pro Trp Pro Gly Asn				
475	480	485	490	
aat gtt cgt gat cat cct gga atg att cag gtc ttc ctt ggc caa agc				1661
Asn Val Arg Asp His Pro Gly Met Ile Gln Val Phe Leu Gly Gln Ser				
495	500	505		

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gga ggc ctt gac tgt gag gga aat gaa ctg cca cga ttg gtt tat gtt Gly Gly Leu Asp Cys Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val 510 515 520	1709
tct aga gag aaa cga cca ggc tat aac cat cat aag aaa gct ggt gct Ser Arg Glu Lys Arg Pro Gly Tyr Asn His His Lys Lys Ala Gly Ala 525 530 535	1757
atg aat gca ttg gtc cga gtc tct gct gta cta aca aat gct cca tat Met Asn Ala Leu Val Arg Val Ser Ala Val Leu Thr Asn Ala Pro Tyr 540 545 550	1805
ttg tta aac ttg gat tgt gat cac tac atc aac aac agc aag gct ata Leu Leu Asn Leu Asp Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Ile 555 560 565 570	1853
aag gaa gca atg tgt ttt atg atg gac cct tta cta gga aag aag gtt Lys Glu Ala Met Cys Phe Met Met Asp Pro Leu Leu Gly Lys Lys Val 575 580 585	1901
tgc tat gta cag ttc cct caa aga ttt gat ggg att gat cgc cat gac Cys Tyr Val Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Arg His Asp 590 595 600	1949
cga tat gct aac cgg aat gtt gtc ttt ttt gat atc aac atg aaa ggt Arg Tyr Ala Asn Arg Asn Val Val Phe Phe Asp Ile Asn Met Lys Gly 605 610 615	1997
ttg gat ggt att cag ggt cca att tat gtt ggt act gga tgt gta ttt Leu Asp Gly Ile Gln Gly Pro Ile Tyr Val Gly Thr Gly Cys Val Phe 620 625 630	2045
aga agg cag gca tta tat ggt tat gat gcc ccc aaa aca aag aag cca Arg Arg Gln Ala Leu Tyr Gly Tyr Asp Ala Pro Lys Thr Lys Lys Pro 635 640 645 650	2093
cca tca agg act tgc aac tgc tgg ccc aag tgg tgc ttt tgc tgt tgc Pro Ser Arg Thr Cys Asn Cys Trp Pro Lys Trp Cys Phe Cys Cys Cys 655 660 665	2141
tgc ttt ggc aat agg aag caa aag aag act acc aaa ccc aaa aca gag Cys Phe Gly Asn Arg Lys Gln Lys Lys Thr Thr Lys Pro Lys Thr Glu 670 675 680	2189
aag aaa aag tta tta ttt ttc aag aaa gaa gag aac caa tcc cct gca Lys Lys Lys Leu Leu Phe Phe Lys Lys Glu Glu Asn Gln Ser Pro Ala 685 690 695	2237
tat gct ctt ggt gaa att gac gaa gct gct cca gga gct gag aat gaa Tyr Ala Leu Gly Glu Ile Asp Glu Ala Ala Pro Gly Ala Glu Asn Glu 700 705 710	2285
aag gcc ggt att gta aat caa caa aaa tta gaa aag aaa ttt ggc caa Lys Ala Gly Ile Val Asn Gln Gln Lys Leu Glu Lys Lys Phe Gly Gln 715 720 725 730	2333
tct tct gtt ttt gtt aca tcc aca ctt ctc gag aat ggt gga acc ttg	2381

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Ser Ser Val Phe Val Thr Ser Thr Leu Leu Glu Asn Gly Gly Thr Leu			
735	740	745	
aag agt gca agt cct gct tct ctt ttg aaa gaa gct ata cat gtc att			2429
Lys Ser Ala Ser Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile			
750	755	760	
agt tgt ggt tat gaa gac aag aca gac tgg gga aaa gag att ggc tgg			2477
Ser Cys Gly Tyr Glu Asp Lys Thr Asp Trp Gly Lys Glu Ile Gly Trp			
765	770	775	
atc tat gga tca gtt aca gaa gat att cta act ggt ttc aag atg cat			2525
Ile Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His			
780	785	790	
tgt cat ggt tgg cgg tca att tac tgc ata cct aaa cgg gtt gca ttc			2573
Cys His Gly Trp Arg Ser Ile Tyr Cys Ile Pro Lys Arg Val Ala Phe			
795	800	805	810
aaa ggt tct gca cct ctg aat ctt tca gat cgt ctt cac cag gtg ctt			2621
Lys Gly Ser Ala Pro Leu Asn Leu Ser Asp Arg Leu His Gln Val Leu			
815	820	825	
cgg tgg gct ctt ggg tct att gag atc ttc ttc agc aat cat tgc cct			2669
Arg Trp Ala Leu Gly Ser Ile Glu Ile Phe Phe Ser Asn His Cys Pro			
830	835	840	
ctt tgg tat ggg tat ggt ggc ggt ctg aaa ttt ttg gaa aga ttt tcc			2717
Leu Trp Tyr Gly Tyr Gly Gly Leu Lys Phe Leu Glu Arg Phe Ser			
845	850	855	
tac atc aac tcc atc gtg tat cct tgg aca tct att ccc ctc ttg gct			2765
Tyr Ile Asn Ser Ile Val Tyr Pro Trp Thr Ser Ile Pro Leu Leu Ala			
860	865	870	
tac tgt aca ttg cct gcc atc tgt tta ttg aca ggg aaa ttt atc act			2813
Tyr Cys Thr Leu Pro Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile Thr			
875	880	885	890
cca gag ctg aat aat gtt gcc agc ctg tgg ttc atg tca ctt ttt atc			2861
Pro Glu Leu Asn Asn Val Ala Ser Leu Trp Phe Met Ser Leu Phe Ile			
895	900	905	
tgc att ttt gct acg agc atc cta gaa atg aga tgg agt ggt gtt gga			2909
Cys Ile Phe Ala Thr Ser Ile Leu Glu Met Arg Trp Ser Gly Val Gly			
910	915	920	
att gat gac tgg tgg agg aat gag cag ttc tgg gtc att gga ggt gtg			2957
Ile Asp Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Val			
925	930	935	
tcc tca cac ctc ttt gct gtg ttc cag gga ctt ctc aag gtc ata gct			3005
Ser Ser His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Ile Ala			
940	945	950	
ggt gtt gat aca agc ttc acc gtg aca tca aag ggt gga gat gat gag			3053
Gly Val Asp Thr Ser Phe Thr Val Thr Ser Lys Gly Gly Asp Asp Glu			
955	960	965	970

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gag ttc tca gag cta tat aca ttc aaa tgg act acc tta ttg ata cct Glu Phe Ser Glu Leu Tyr Thr Phe Lys Trp Thr Thr Leu Leu Ile Pro	975	980	985	3101	
cct acc acc ttg ctt cta ttg aac ttc att ggt gtg gtc gct ggc gtt Pro Thr Thr Leu Leu Leu Asn Phe Ile Gly Val Val Ala Gly Val	990	995	1000	3149	
tca aat gcg atc aat aac gga tat gag tca tgg ggc ccc ctc ttt ggg Ser Asn Ala Ile Asn Asn Gly Tyr Glu Ser Trp Gly Pro Leu Phe Gly	1005	1010	1015	3197	
aag cta ttc ttt gca ttt tgg gtg att gtc cat ctt tat ccc ttt ctc Lys Leu Phe Phe Ala Phe Trp Val Ile Val His Leu Tyr Pro Phe Leu	1020	1025	1030	3245	
aaa ggt ttg gtt gga agg caa aac agg aca cca acg att gtc atc gtc Lys Gly Leu Val Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val	1035	1040	1045	1050	3293
tgg tcc att ctg ctg gct tca atc ttc tcg ctc ctt tgg gtt cgg att Trp Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Arg Ile	1055	1060	1065	3341	
gat cct ttc ctt gcg aag gat gat ggt ccg ctt ctt gag gag tgg tgg Asp Pro Phe Leu Ala Lys Asp Asp Gly Pro Leu Leu Glu Glu Cys Gly	1070	1075	1080	3389	
ttg gat tgc a actaggatgt cagtgcatac gctccccaa tctgcataatg Leu Asp Cys	1085			3439	
cttgaagtat atttcttgtt gtttgtcccc atattcagtgc tctgttagata agagacatga aatgtcccaa gtttcttttgc atccatgggtt aacctactta atatctgaga gatatactgg				3499	
ggggaaatgg aggctgcggc aatccttgc cagttgggcc gtgaaataca gcatacgaa				3559	
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Leu Val Val Ile Arg Arg Asp Gly Asp Pro Gly Pro Lys Pro Pro Arg					
20 25 30					
Glu Gln Asn Gly Gln Val Cys Gln Ile Cys Gly Asp Asp Val Gly Leu					
35 40 45					
Ala Pro Gly Gly Asp Pro Phe Val Ala Cys Asn Glu Cys Ala Phe Pro					
50 55 60					
Val Cys Arg Asp Cys Tyr Glu Tyr Glu Arg Arg Glu Gly Thr Gln Asn					

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65	70	75	80
Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Leu Lys Gly Cys Gln Arg			
85	90	95	
Val Thr Gly Asp Glu Glu Asp Gly Val Asp Asp Leu Asp Asn Glu			
100	105	110	
Phe Asn Trp Asp Gly His Asp Ser Gln Ser Val Ala Glu Ser Met Leu			
115	120	125	
Tyr Gly His Met Ser Tyr Gly Arg Gly Gly Asp Pro Asn Gly Ala Pro			
130	135	140	
Gln Ala Phe Gln Leu Asn Pro Asn Val Pro Leu Leu Thr Asn Gly Gln			
145	150	155	160
Met Val Asp Asp Ile Pro Pro Glu Gln His Ala Leu Val Pro Ser Phe			
165	170	175	
Met Gly Gly Gly Lys Arg Ile His Pro Leu Pro Tyr Ala Asp Pro			
180	185	190	
Ser Leu Pro Val Gln Pro Arg Ser Met Asp Pro Ser Lys Asp Leu Ala			
195	200	205	
Ala Tyr Gly Tyr Gly Ser Val Ala Trp Lys Glu Arg Met Glu Asn Trp			
210	215	220	
Lys Gln Arg Gln Glu Arg Met His Gln Thr Gly Asn Asp Gly Gly			
225	230	235	240
Asp Asp Gly Asp Asp Ala Asp Leu Pro Leu Met Asp Glu Ala Arg Gln			
245	250	255	
Gln Leu Ser Arg Lys Ile Pro Leu Pro Ser Ser Gln Ile Asn Pro Tyr			
260	265	270	
Arg Met Ile Ile Ile Ile Arg Leu Val Val Leu Gly Phe Phe His			
275	280	285	
Tyr Arg Val Met His Pro Val Asn Asp Ala Phe Ala Leu Trp Leu Ile			
290	295	300	
Ser Val Ile Cys Glu Ile Trp Phe Ala Met Ser Trp Ile Leu Asp Gln			
305	310	315	320
Phe Pro Lys Trp Phe Pro Ile Glu Arg Glu Thr Tyr Leu Asp Arg Leu			
325	330	335	
Ser Leu Arg Phe Asp Lys Glu Gly Gln Pro Ser Gln Leu Ala Pro Ile			
340	345	350	
Asp Phe Phe Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Val			
355	360	365	
Thr Thr Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr Pro Val Asp			
370	375	380	
Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ala Ala Met Leu Thr Phe			
385	390	395	400
Glu Ala Leu Ser Glu Thr Ser Glu Phe Ala Lys Lys Trp Val Pro Phe			
405	410	415	
Cys Lys Arg Tyr Asn Ile Glu Pro Arg Ala Pro Glu Trp Tyr Phe Gln			
420	425	430	
Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val Ala Ala Asn Phe Val Arg			
435	440	445	
Glu Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg Ile			
450	455	460	
Asn Ala Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr			
465	470	475	480
Met Gln Asp Gly Thr Pro Trp Pro Gly Asn Asn Val Arg Asp His Pro			
485	490	495	
Gly Met Ile Gln Val Phe Leu Gly Gln Ser Gly Gly Leu Asp Cys Glu			
500	505	510	
Gly Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro			
515	520	525	
Gly Tyr Asn His His Lys Lys Ala Gly Ala Met Asn Ala Leu Val Arg			

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530	535	540
Val Ser Ala Val Leu Thr Asn Ala Pro Tyr	Leu Leu Asn Leu Asp Cys	
545	550	555
Asp His Tyr Ile Asn Asn Ser Lys Ala Ile Lys Glu Ala Met Cys Phe		560
565	570	575
Met Met Asp Pro Leu Leu Gly Lys Lys Val Cys Tyr Val Gln Phe Pro		
580	585	590
Gln Arg Phe Asp Gly Ile Asp Arg His Asp Arg Tyr Ala Asn Arg Asn		
595	600	605
Val Val Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly		
610	615	620
Pro Ile Tyr Val Gly Thr Gly Cys Val Phe Arg Arg Gln Ala Leu Tyr		
625	630	635
Gly Tyr Asp Ala Pro Lys Thr Lys Lys Pro Pro Ser Arg Thr Cys Asn		640
645	650	655
Cys Trp Pro Lys Trp Cys Phe Cys Cys Cys Phe Gly Asn Arg Lys		
660	665	670
Gln Lys Lys Thr Thr Lys Pro Lys Thr Glu Lys Lys Lys Leu Leu Phe		
675	680	685
Phe Lys Lys Glu Glu Asn Gln Ser Pro Ala Tyr Ala Leu Gly Glu Ile		
690	695	700
Asp Glu Ala Ala Pro Gly Ala Glu Asn Glu Lys Ala Gly Ile Val Asn		
705	710	715
Gln Gln Lys Leu Glu Lys Lys Phe Gly Gln Ser Ser Val Phe Val Thr		
725	730	735
Ser Thr Leu Leu Glu Asn Gly Gly Thr Leu Lys Ser Ala Ser Pro Ala		
740	745	750
Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly Tyr Glu Asp		
755	760	765
Lys Thr Asp Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly Ser Val Thr		
770	775	780
Glu Asp Ile Leu Thr Gly Phe Lys Met His Cys His Gly Trp Arg Ser		
785	790	795
Ile Tyr Cys Ile Pro Lys Arg Val Ala Phe Lys Gly Ser Ala Pro Leu		800
805	810	815
Asn Leu Ser Asp Arg Leu His Gln Val Leu Arg Trp Ala Leu Gly Ser		
820	825	830
Ile Glu Ile Phe Phe Ser Asn His Cys Pro Leu Trp Tyr Gly Tyr Gly		
835	840	845
Gly Gly Leu Lys Phe Leu Glu Arg Phe Ser Tyr Ile Asn Ser Ile Val		
850	855	860
Tyr Pro Trp Thr Ser Ile Pro Leu Leu Ala Tyr Cys Thr Leu Pro Ala		
865	870	875
Ile Cys Leu Leu Thr Gly Lys Phe Ile Thr Pro Glu Leu Asn Asn Val		880
885	890	895
Ala Ser Leu Trp Phe Met Ser Leu Phe Ile Cys Ile Phe Ala Thr Ser		
900	905	910
Ile Leu Glu Met Arg Trp Ser Gly Val Gly Ile Asp Asp Trp Trp Arg		
915	920	925
Asn Glu Gln Phe Trp Val Ile Gly Gly Val Ser Ser His Leu Phe Ala		
930	935	940
Val Phe Gln Gly Leu Leu Lys Val Ile Ala Gly Val Asp Thr Ser Phe		
945	950	955
Thr Val Thr Ser Lys Gly Gly Asp Asp Glu Glu Phe Ser Glu Leu Tyr		960
965	970	975
Thr Phe Lys Trp Thr Thr Leu Leu Ile Pro Pro Thr Thr Leu Leu Leu		
980	985	990
Leu Asn Phe Ile Gly Val Val Ala Gly Val Ser Asn Ala Ile Asn Asn		

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995	1000	1005
Gly Tyr Glu Ser Trp Gly Pro Leu Phe Gly Lys Leu Phe Phe Ala Phe		
1010	1015	1020
Trp Val Ile Val His Leu Tyr Pro Phe Leu Lys Gly Leu Val Gly Arg		
1025	1030	1035
Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser Ile Leu Leu Ala		
1045	1050	1055
Ser Ile Phe Ser Leu Leu Trp Val Arg Ile Asp Pro Phe Leu Ala Lys		
1060	1065	1070
Asp Asp Gly Pro Leu Leu Glu Glu Cys Gly Leu Asp Cys Asn		
1075	1080	1085

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25

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cgccggcctc gtccgtgtcg gtggagtgtg aatcggtgtg ttagggaga ggcggag	178		
atg gcg gcc aac aag ggg atg gtg gca ggc tct cac aac cgc aac gag	226		
Met Ala Ala Asn Lys Gly Met Val Ala Gly Ser His Asn Arg Asn Glu			
1 5 10 15			

ttc gtc atg atc cgc cac gac ggc gac gcg cct gtc ccg gct aag ccc	274
Phe Val Met Ile Arg His Asp Gly Asp Ala Pro Val Pro Ala Lys Pro	
20 25 30	

acg aag agt gcg aat ggg cag gtc tgc cag att tgt ggc gac act gtt	322
Thr Lys Ser Ala Asn Gly Gln Val Cys Gln Ile Cys Gly Asp Thr Val	
35 40 45	

ggc gtt tca gcc act ggt gat gtc ttt gtt gcc tgc aat gag tgt gcc	370
Gly Val Ser Ala Thr Gly Asp Val Phe Val Ala Cys Asn Glu Cys Ala	
50 55 60	

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ttc cct gtc tgc cgc cct tgc tat gag tac gag cgc aag gaa ggg aac Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Glu Gly Asn 65 70 75 80	418
caa tgc tgc cct cag tgc aag act aga tac aag aga cag aaa ggt agc Gln Cys Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Gln Lys Gly Ser 85 90 95	466
cct cga gtt cat ggt gat gat gag gag gaa gat gtt gat gac ctg gac Pro Arg Val His Gly Asp Asp Glu Glu Asp Val Asp Asp Leu Asp 100 105 110	514
aat gaa ttc aac tat aag caa ggc aat ggg aag ggc cca gag tgg cag Asn Glu Phe Asn Tyr Lys Gln Gly Asn Lys Gly Pro Glu Trp Gln 115 120 125	562
ctt caa gga gat gac gct gat ctg tct tca tct gct cgc cat gac cca Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ala Arg His Asp Pro 130 135 140	610
cac cat cgg att cca cgc ctt aca agt gga caa cag ata tct gga gag His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly Glu 145 150 155 160	658
atc cct gat gca tcc cct gac cgt cat tct atc cgc agt cca aca tcg Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr Ser 165 170 175	706
agc tat gtt gat cca agc gtt cca gtt cct gtg agg att gtg gac ccc Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp Pro 180 185 190	754
tgc aag gac ttg aat tcc tat ggg ctt aat agt gtt gac tgg aag gaa Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys Glu 195 200 205	802
aga gtt gag agc tgg agg gtt aaa cag gac aaa aat atg ttg caa gtg Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Leu Gln Val 210 215 220	850
act aat aaa tat cca gag gct aga gga gac atg gag ggg act ggc tca Thr Asn Lys Tyr Pro Glu Ala Arg Gly Asp Met Glu Gly Thr Gly Ser 225 230 235 240	898
aat gga gaa gat atg caa atg gtt gat gat gca cgc cta cct ttg agc Asn Gly Glu Asp Met Gln Met Val Asp Asp Ala Arg Leu Pro Leu Ser 245 250 255	946
cgc att gtg cca att tcc tca aac cag ctc aac ctt tac cgg ata gta Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg Ile Val 260 265 270	994
atc att ctc cgt ctt atc atc ctg tgc ttc ttc caa tat cgt atc Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe Phe Phe Gln Tyr Arg Ile 275 280 285	1042
agt cat cca gtg cgt aat gct tat gga ttg tgg cta gta tct gtt atc	1090

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Ser His Pro Val Arg Asn Ala Tyr Gly Leu Trp Leu Val Ser Val Ile			
290	295	300	
tgt gag gtc tgg ttt gcc ttg tcc tgg ctt cta gat cag ttc cca aaa			1138
Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe Pro Lys			
305	310	315	320
tgg tat cca atc aac cgt gag aca tat ctc gac agg ctt gca ttg agg			1186
Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu Arg			
325	330	335	
tat gat aga gag gga gag cca tca cag ctg gct ccc att gat gtc ttt			1234
Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp Val Phe			
340	345	350	
gtc agt aca gtg gat cca ttg aag gaa cct cca ctg atc aca gcc aac			1282
Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr Ala Asn			
355	360	365	
act gtt ttg tcc att ctt gct gtg gat tac cct gtt gac aaa gtg tca			1330
Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val Asp Lys Val Ser			
370	375	380	
tgc tat gtt tct gat gat ggc tca gct atg ctg act ttt gag tct ctc			1378
Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu Ser Leu			
385	390	395	400
tct gaa act gcc gaa ttt gct aga aag tgg gtt ccc ttt tgt aag aag			1426
Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys Lys			
405	410	415	
cac aat att gaa cca aga gct cca gaa ttt tac ttt gct caa aaa ata			1474
His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln Lys Ile			
420	425	430	
gat tac ctg aag gac aaa att caa cct tca ttt gtt aag gaa aga cga			1522
Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu Arg Arg			
435	440	445	
gca atg aag aga gag tat gaa gaa ttc aaa ata aga atc aat gcc ctt			1570
Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Ile Arg Ile Asn Ala Leu			
450	455	460	
gtt gcc aaa gca cag aaa gtg cct gaa gag ggg tgg acc atg gct gat			1618
Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met Ala Asp			
465	470	475	480
gga act gct tgg cct ggg aat aac cct agg gac cat cct ggc atg att			1666
Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met Ile			
485	490	495	
cag gtg ttc ttg ggg cac agt ggt ggg ctt gac act gat gga aat gaa			1714
Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn Glu			
500	505	510	
tta cca cgt ctt gtc tat gtc tct cgt gaa aag aga cca ggc ttt cag			1762
Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe Gln			
515	520	525	

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cat cac aag aag gct ggt gca atg aat gca ctg att cgt gta tct gct His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser Ala 530 535 540	1810
gtg ctg aca aat ggt gcc tat ctt ctc aat gtg gat tgt gac cat tac Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His Tyr 545 550 555 560	1858
ttc aat agc agc aaa gct ctt aga gaa gca atg tgc ttc atg atg gat Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met Asp 565 570 575	1906
cca gct cta gga agg aaa act tgt tat gta caa ttt cca caa aga ttt Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg Phe 580 585 590	1954
gat ggc att gac ttg cac gat cga tat gct aat agg aac ata gtc ttc Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val Phe 595 600 605	2002
ttt gat atc aac atg aaa ggt cta gat ggc att cag ggt cca gtc tat Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val Tyr 610 615 620	2050
gtg gga aca gga tgc tgt ttg aat agg cag gct ttg tat gga tat gat Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr Asp 625 630 635 640	2098
cct gtt ttg act gaa gct gat ctg gaa cct aac att gtt gtt aag agc Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Val Lys Ser 645 650 655	2146
tgc tgt ggt aga agg aag aga aag aac aag agt tat atg gat agt caa Cys Cys Gly Arg Arg Lys Arg Lys Asn Lys Ser Tyr Met Asp Ser Gln 660 665 670	2194
agc cgt att atg aag aga aca gaa tct tca gct ccc atc ttt aac atg Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn Met 675 680 685	2242
gaa gac atc gag gag ggt att gaa ggt tat gag gat gaa agg tca gtg Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser Val 690 695 700	2290
ctt atg tcc cag agg aaa ttg gag aaa cgc ttt ggt cag tct cca atc Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro Ile 705 710 715 720	2338
tcc att gca tcc acc ttt atg act caa ggt ggc ata cca cct tca aca Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser Thr 725 730 735	2386
aac cca gct tct cta ctg aag gaa gct atc cat gtt atc agc tgt ggg Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly 740 745 750	2434
tac gag gac aaa act gaa tgg gga aaa gag att ggc tgg atc tat ggt	2482

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Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly		
755	760	765
tca gtt aca gag gat att ctg act ggg ttt aaa atg cat gca aga ggc		2530
Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg Gly		
770	775	780
tgg caa tca atc tac tgc atg cca cca cga cct tgt ttc aag ggt tct		2578
Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly Ser		
785	790	795
gca cca atc aat ctt tct gat cgt ctt aat cag gtg ctc cgt tgg gct		2626
Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp Ala		
805	810	815
ctt ggg tca gtg gaa att ctg ctt agc aga cat tgt cct ata tgg tat		2674
Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile Trp Tyr		
820	825	830
ggc tac aat ggg cga ttg aag ctt ttg gag agg ctg gct tac att aac		2722
Gly Tyr Asn Gly Arg Leu Lys Leu Glu Arg Leu Ala Tyr Ile Asn		
835	840	845
acc att gtt tat cca atc aca tct gtt ccg ctt atc gcc tat tgt gtg		2770
Thr Ile Val Tyr Pro Ile Thr Ser Val Pro Leu Ile Ala Tyr Cys Val		
850	855	860
ctt cct gct atc tgt ctt ctt acc aat aaa ttt atc att cct gag att		2818
Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu Ile		
865	870	875
880		
agt aat tat gct gga atg ttc ttc att ctt ctt ttt gcc tcc att ttc		2866
Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile Phe		
885	890	895
gca act ggt ata ttg gag ctc aga tgg agt ggt gtt ggc att gaa gat		2914
Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu Asp		
900	905	910
tgg tgg aga aat gag cag ttt tgg gtt att ggt ggc acc tct gcc cat		2962
Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala His		
915	920	925
ctc ttc gcg gtg ttc cag ggt ctg ctg aaa gtg ttg gct ggg att gat		3010
Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile Asp		
930	935	940
acc aac ttc aca gtt acc tca aag gca tct gat gag gat ggc gac ttt		3058
Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp Phe		
945	950	955
960		
gct gag cta tat gtg ttc aag tgg acc agt ttg ctc atc cct ccg acc		3106
Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro Thr		
965	970	975
act gtt ctt gtc att aac ctg gtc gga atg gtg gca gga att tcg tat		3154
Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser Tyr		
980	985	990

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gcc att aac agc ggc tac caa tcc tgg ggt ccg ctc ttt gga aag ctg Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys Leu 995 1000 1005	3202
ttc ttc tcg atc tgg gtg atc ctc cat ctc tac ccc ttc ctc aag ggt Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys Gly 1010 1015 1020	3250
ctc atg ggc agg cag aac cgc acg cca aca atc gtc atc gtt tgg tcc Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser 1025 1030 1035 1040	3298
atc ctc ctt gcg tct atc ttc tcc ttg ctg tgg gtg aag atc gat cct Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp Pro 1045 1050 1055	3346
ttc atc tcc ccg aca cag aaa gct gcc gcc ttg ggg caa tgt ggt gtg Phe Ile Ser Pro Thr Gln Lys Ala Ala Leu Gly Gln Cys Gly Val 1060 1065 1070	3394
aac t gctgatccag attgtgactc ttatctgaag aggctcagcc aaagatctgc Asn	3448
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 <400> 42 Met Ala Ala Asn Lys Gly Met Val Ala Gly Ser His Asn Arg Asn Glu 1 5 10 15 Phe Val Met Ile Arg His Asp Gly Asp Ala Pro Val Pro Ala Lys Pro 20 25 30 Thr Lys Ser Ala Asn Gly Gln Val Cys Gln Ile Cys Gly Asp Thr Val 35 40 45 Gly Val Ser Ala Thr Gly Asp Val Phe Val Ala Cys Asn Glu Cys Ala 50 55 60 Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Glu Gly Asn 65 70 75 80 Gln Cys Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Gln Lys Gly Ser 85 90 95 Pro Arg Val His Gly Asp Asp Glu Glu Asp Val Asp Asp Leu Asp 100 105 110 Asn Glu Phe Asn Tyr Lys Gln Gly Asn Gly Lys Gly Pro Glu Trp Gln 115 120 125 Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ser Ala Arg His Asp Pro 130 135 140 His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly Glu 145 150 155 160 Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr Ser	

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	165	170	175
Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp Pro			
180	185	190	
Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys Glu			
195	200	205	
Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Leu Gln Val			
210	215	220	
Thr Asn Lys Tyr Pro Glu Ala Arg Gly Asp Met Glu Gly Thr Gly Ser			
225	230	235	240
Asn Gly Glu Asp Met Gln Met Val Asp Asp Ala Arg Leu Pro Leu Ser			
245	250	255	
Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg Ile Val			
260	265	270	
Ile Ile Leu Arg Leu Ile Ile Leu Cys Phe Phe Phe Gln Tyr Arg Ile			
275	280	285	
Ser His Pro Val Arg Asn Ala Tyr Gly Leu Trp Leu Val Ser Val Ile			
290	295	300	
Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe Pro Lys			
305	310	315	320
Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu Arg			
325	330	335	
Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp Val Phe			
340	345	350	
Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr Ala Asn			
355	360	365	
Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val Asp Lys Val Ser			
370	375	380	
Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu Ser Leu			
385	390	395	400
Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys Lys			
405	410	415	
His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln Lys Ile			
420	425	430	
Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu Arg Arg			
435	440	445	
Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Ile Arg Ile Asn Ala Leu			
450	455	460	
Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp Thr Met Ala Asp			
465	470	475	480
Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met Ile			
485	490	495	
Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn Glu			
500	505	510	
Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe Gln			
515	520	525	
His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser Ala			
530	535	540	
Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His Tyr			
545	550	555	560
Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met Asp			
565	570	575	
Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg Phe			
580	585	590	
Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val Phe			
595	600	605	
Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val Tyr			
610	615	620	
Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr Asp			

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625	630	635	640
Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Val Lys Ser			
645	650	655	
Cys Cys Gly Arg Arg Lys Arg Lys Asn Lys Ser Tyr Met Asp Ser Gln			
660	665	670	
Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn Met			
675	680	685	
Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser Val			
690	695	700	
Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro Ile			
705	710	715	720
Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser Thr			
725	730	735	
Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly			
740	745	750	
Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly			
755	760	765	
Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg Gly			
770	775	780	
Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly Ser			
785	790	795	800
Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp Ala			
805	810	815	
Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile Trp Tyr			
820	825	830	
Gly Tyr Asn Gly Arg Leu Lys Leu Glu Arg Leu Ala Tyr Ile Asn			
835	840	845	
Thr Ile Val Tyr Pro Ile Thr Ser Val Pro Leu Ile Ala Tyr Cys Val			
850	855	860	
Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu Ile			
865	870	875	880
Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile Phe			
885	890	895	
Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu Asp			
900	905	910	
Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala His			
915	920	925	
Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile Asp			
930	935	940	
Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp Phe			
945	950	955	960
Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro Thr			
965	970	975	
Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser Tyr			
980	985	990	
Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys Leu			
995	1000	1005	
Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys Gly			
1010	1015	1020	
Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser			
1025	1030	1035	1040
Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp Pro			
1045	1050	1055	
Phe Ile Ser Pro Thr Gln Lys Ala Ala Leu Gly Gln Cys Gly Val			
1060	1065	1070	
Asn Cys			

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<210> 43

<211> 25

<212> DNA

<213> Zea mays

<400> 43

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25

<210> 44

<211> 25

<212> DNA

<213> Zea mays

<400> 44

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25

<210> 45

<211> 3813

<212> DNA

<213> Zea mays

<220>

<221> CDS

<222> (215) ... (3494)

<400> 45

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agcacaaccc ccacccgcca cagccgcgtg	cgcacgtgag	cggtcgcgc	ggccgggaga	120
ccagaggagg ggaggactac gtgcatttcg	ctgtgcgc	gccgcgggtt	tgcgtgcgcga	180
gcgagatccg gcgccccccgg	gcggggcc	tgag atg gag	gct agc gcg ggg ctg	235
		Met Glu Ala Ser	Ala Gly Leu	
		1	5	

gtg gcc ggc tcg cat aac cgg aac	ctg gtg	atc cgc cgc gac	283
Val Ala Gly Ser His Asn Arg Asn	Glu Leu Val Val Ile Arg Arg Asp		
10	15	20	

cgc gag tcg gga gcc gcg ggc ggc	gag gtc	gag gtc	331
Arg Glu Ser Gly Ala Ala Gly Gly	Ala Ala Arg Arg	Ala Glu Ala	
25	30	35	

ccg tgc cag ata tgc ggc gac	gag gtc	ggg gtg ggc ttc	gac ggg gag	379
Pro Cys Gln Ile Cys Gly Asp	Glu Val Gly Val	Gly Phe Asp Gly	Glu	
40	45	50	55	

ccc ttc gtg gcg tgc aac gag	tgc gcc ttc	ccc gtc tgc cgc	gcc tgc	427
Pro Phe Val Ala Cys Asn Glu	Cys Ala Phe Pro	Val Cys Arg	Ala Cys	
60	65	70		

tac gag tac gag cgc cgc gag	ggc tgc caa	gag tgc ccg cag tgc agg	475
Tyr Glu Tyr Glu Arg Arg	Glu Gly Ser Gln	Ala Cys Pro Gln Cys Arg	
75	80	85	

acc cgc tac aag cgc ctc aag	ggc tgc ccg cgg	gtg gcc ggc gac gag	523
Thr Arg Tyr Lys Arg Leu Lys	Gly Cys Pro Arg	Val Ala Gly Asp Glu	
90	95	100	

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gag gag gac ggc gtc gac gac ctg gag ggc gag ttc ggc ctg cag gac Glu Glu Asp Gly Val Asp Asp Leu Glu Gly Glu Phe Gly Leu Gln Asp 105 110 115	571
ggc gcc gcc cac gag gac gac ccg cag tac gtc gcc gag tcc atg ctc Gly Ala Ala His Glu Asp Asp Pro Gln Tyr Val Ala Glu Ser Met Leu 120 125 130 135	619
agg gcg cag atg agc tac ggc cgc ggc gac gcg cac ccc ggc ttc Arg Ala Gln Met Ser Tyr Gly Arg Gly Asp Ala His Pro Gly Phe 140 145 150	667
agc ccc gtc ccc aac gtg ccg ctc acc aac ggc cag atg gtt gat Ser Pro Val Pro Asn Val Pro Leu Leu Thr Asn Gly Gln Met Val Asp 155 160 165	715
gac atc ccg ccg gag cag cac gcg ctc gtg ccg tcc tac atg agc ggc Asp Ile Pro Pro Glu Gln His Ala Leu Val Pro Ser Tyr Met Ser Gly 170 175 180	763
ggc ggc ggc ggg ggc aag agg atc cac ccg ctc cct ttc gca gat ccc Gly Gly Gly Gly Lys Arg Ile His Pro Leu Pro Phe Ala Asp Pro 185 190 195	811
aac ctt cca gtg caa ccg aga tcc atg gac ccg tcc aag gat ctg gcc Asn Leu Pro Val Gln Pro Arg Ser Met Asp Pro Ser Lys Asp Leu Ala 200 205 210 215	859
gcc tac gga tat ggc agc gtg gcc tgg aag gag aga atg gag ggc tgg Ala Tyr Gly Tyr Gly Ser Val Ala Trp Lys Glu Arg Met Glu Gly Trp 220 225 230	907
aag cag aag cag gag cgc ctg cag cat gtc agg agc gag ggt ggc ggt Lys Gln Lys Gln Glu Arg Leu Gln His Val Arg Ser Glu Gly Gly 235 240 245	955
gat tgg gat ggc gac gat gca gat ctg cca cta atg gat gaa gct agg Asp Trp Asp Gly Asp Asp Ala Asp Leu Pro Leu Met Asp Glu Ala Arg 250 255 260	1003
cag cca ttg tcc aga aaa gtc cct ata tca tca agc cga att aat ccc Gln Pro Leu Ser Arg Lys Val Pro Ile Ser Ser Arg Ile Asn Pro 265 270 275	1051
tac agg atg att atc gtt atc ccg ttg gtg gtt ttg ggt ttc ttc ttc Tyr Arg Met Ile Ile Val Ile Arg Leu Val Val Leu Gly Phe Phe Phe 280 285 290 295	1099
cac tac cga gtg atg cat ccg gcg aaa gat gca ttt gca ttg tgg ctc His Tyr Arg Val Met His Pro Ala Lys Asp Ala Phe Ala Leu Trp Leu 300 305 310	1147
ata tct gta atc tgt gaa atc tgg ttt gcg atg tcc tgg att ctt gat Ile Ser Val Ile Cys Glu Ile Trp Phe Ala Met Ser Trp Ile Leu Asp 315 320 325	1195
cag ttc cca aag tgg ctt cca atc gag aga gag act tac ctg gac cgt	1243

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Gln Phe Pro Lys Trp Leu Pro Ile Glu Arg Glu Thr Tyr Leu Asp Arg			
330	335	340	
ttg tca cta agg ttt gac aag gaa ggt caa ccc tct cag ctt gct cca			1291
Leu Ser Leu Arg Phe Asp Lys Glu Gly Gln Pro Ser Gln Leu Ala Pro			
345	350	355	
atc gac ttc ttt gtc agt acg gtt gat ccc aca aag gaa cct ccc ttg			1339
Ile Asp Phe Phe Val Ser Thr Val Asp Pro Thr Lys Glu Pro Pro Leu			
360	365	370	375
gtc aca gcg aac act gtc ctt tcc atc ctt tct gtg gat tat ccg gtt			1387
Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr Pro Val			
380	385	390	
gag aag gtc tcc tgc tat gtt tct gat gat ggt gct gca atg ctt acg			1435
Glu Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ala Ala Met Leu Thr			
395	400	405	
ttt gaa gca ttg tct gaa aca tct gaa ttt gca aag aaa tgg gtt cct			1483
Phe Glu Ala Leu Ser Glu Thr Ser Glu Phe Ala Lys Lys Trp Val Pro			
410	415	420	
ttc agc aaa aag ttt aat atc gag cct cgt gct cct gag tgg tac ttc			1531
Phe Ser Lys Phe Asn Ile Glu Pro Arg Ala Pro Glu Trp Tyr Phe			
425	430	435	
caa cag aag ata gac tac ctg aaa gac aag gtt gct gct tca ttt gtt			1579
Gln Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val Ala Ala Ser Phe Val			
440	445	450	455
agg gag agg agg gcg atg aag aga gaa tac gag gaa ttc aag gta agg			1627
Arg Glu Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg			
460	465	470	
atc aat gcc ttg gtt gca aaa gcc caa aag gtt cct gag gaa gga tgg			1675
Ile Asn Ala Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp			
475	480	485	
aca atg caa gat gga agc ccc tgg cct gga aac aac gta cgc gat cat			1723
Thr Met Gln Asp Gly Ser Pro Trp Pro Gly Asn Asn Val Arg Asp His			
490	495	500	
cct gga atg att cag gta ttc ctt ggc caa agt ggc ggt cgt gat gtg			1771
Pro Gly Met Ile Gln Val Phe Leu Gly Gln Ser Gly Gly Arg Asp Val			
505	510	515	
gaa gga aat gag ttg cct cgc ctg gtt tat gtc tcg aga gaa aag agg			1819
Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg			
520	525	530	535
cca ggt tat aac cat cac aag aag gct ggt gcc atg aat gca ctg gtc			1867
Pro Gly Tyr Asn His His Lys Lys Ala Gly Ala Met Asn Ala Leu Val			
540	545	550	
cgt gtc tct gct gtc tta tca aat gct gca tac cta ttg aac ttg gac			1915
Arg Val Ser Ala Val Leu Ser Asn Ala Ala Tyr Leu Leu Asn Leu Asp			
555	560	565	

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tgt gat cac tac atc aac aat agc aag gcc ata aaa gag gct atg tgt Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Ile Lys Glu Ala Met Cys 570 575 580	1963
ttc atg atg gat cct ttg gtg ggg aag aaa gtg tgc tat gta cag ttc Phe Met Met Asp Pro Leu Val Gly Lys Lys Val Cys Tyr Val Gln Phe 585 590 595	2011
cct cag agg ttt gat ggt att gac aaa aat gat cga tac gct aac agg Pro Gln Arg Phe Asp Gly Ile Asp Lys Asn Asp Arg Tyr Ala Asn Arg 600 605 610 615	2059
aac gtt gtc ttt ttt gac atc aac atg aaa ggt ttg gac ggt att caa Asn Val Val Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln 620 625 630	2107
gga ccc att tat gtg ggt act gga tgg ttc aga cgg cag gca ctg Gly Pro Ile Tyr Val Gly Thr Gly Cys Val Phe Arg Arg Gln Ala Leu 635 640 645	2155
tat ggt tat gat gct cct aaa acg aag cca cca tca aga act tgc Tyr Gly Tyr Asp Ala Pro Lys Thr Lys Lys Pro Pro Ser Arg Thr Cys 650 655 660	2203
aac tgc tgg ccc aag tgg tgc ctc tct tgc tgc agc agg aac aag Asn Cys Trp Pro Lys Trp Cys Leu Ser Cys Cys Ser Arg Asn Lys 665 670 675	2251
aat aaa aag aag act aca aaa cca aag acg gag aag aag aaa aga tta Asn Lys Lys Lys Thr Thr Lys Pro Lys Thr Glu Lys Lys Lys Arg Leu 680 685 690 695	2299
ttt ttc aag aaa gca gaa aac cca tct cct gca tat gct ttg ggt gaa Phe Phe Lys Lys Ala Glu Asn Pro Ser Pro Ala Tyr Ala Leu Gly Glu 700 705 710	2347
att gat gaa ggt gct cca ggt gct gat atc gag aag gcc gga atc gta Ile Asp Glu Gly Ala Pro Gly Ala Asp Ile Glu Lys Ala Gly Ile Val 715 720 725	2395
aat caa cag aaa cta gag aag aaa ttt ggg cag tct tct gtt ttt gtc Asn Gln Lys Leu Glu Lys Phe Gly Gln Ser Ser Val Phe Val 730 735 740	2443
gca tca aca ctt ctt gag aac gga ggg acc ctg aag agc gca agt cca Ala Ser Thr Leu Leu Glu Asn Gly Gly Thr Leu Lys Ser Ala Ser Pro 745 750 755	2491
gct tct ctt ctg aag gaa gct ata cat gtt atc agc tgc ggc tac gaa Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys Gly Tyr Glu 760 765 770 775	2539
gac aag acc gac tgg gga aaa gag att ggc tgg att tac gga tcg atc Asp Lys Thr Asp Trp Gly Lys Glu Ile Gly Trp Ile Tyr Gly Ser Ile 780 785 790	2587
aca gag gat atc ttg act gga ttt aag atg cac tgc cat ggc tgg cgg	2635

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Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Cys His Gly Trp Arg				
795	800	805		
tct att tac tgc atc ccg aag cgg cct gca ttc aaa ggt tct gcg cct				2683
Ser Ile Tyr Cys Ile Pro Lys Arg Pro Ala Phe Lys Gly Ser Ala Pro				
810	815	820		
ctg aac ctt tcc gac cgt ctt cac cag gtc ctt cgc tgg gcc ctt ggg				2731
Leu Asn Leu Ser Asp Arg Leu His Gln Val Leu Arg Trp Ala Leu Gly				
825	830	835		
tcc gtc gaa att ttc ttc agc aag cac tgc cca ctt tgg tac gga tac				2779
Ser Val Glu Ile Phe Phe Ser Lys His Cys Pro Leu Trp Tyr Gly Tyr				
840	845	850	855	
ggc ggc ggg cta aaa ttc ctg gaa agg ttt tct tat atc aac tcc atc				2827
Gly Gly Leu Lys Phe Leu Glu Arg Phe Ser Tyr Ile Asn Ser Ile				
860	865	870		
gtt tat ccc tgg acg tcc att cct ctc ctg gct tac tgt acc ttg cct				2875
Val Tyr Pro Trp Thr Ser Ile Pro Leu Leu Ala Tyr Cys Thr Leu Pro				
875	880	885		
gcc atc tgc ctg ctc acg ggg aag ttt atc aca cca gag ctt acc aat				2923
Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile Thr Pro Glu Leu Thr Asn				
890	895	900		
gtc gcc agt atc tgg ttc atg gca ctt ttc atc tgc atc tcc gtg acc				2971
Val Ala Ser Ile Trp Phe Met Ala Leu Phe Ile Cys Ile Ser Val Thr				
905	910	915		
ggc atc ctg gaa atg agg tgg agt ggc gtg gcc atc gac gac tgg tgg				3019
Gly Ile Leu Glu Met Arg Trp Ser Gly Val Ala Ile Asp Asp Trp Trp				
920	925	930	935	
agg aac gag cag ttc tgg gtc atc gga ggc gtt tcg gcg cat ctg ttc				3067
Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Val Ser Ala His Leu Phe				
940	945	950		
gcg gtg ttc cag ggc ctg ctg aag gtg ttc gcc ggc atc gac acg agc				3115
Ala Val Phe Gln Gly Leu Leu Lys Val Phe Ala Gly Ile Asp Thr Ser				
955	960	965		
ttc acc gtg acg tcg aag gcc ggg gac gac gag gag ttc tcg gag ctg				3163
Phe Thr Val Thr Ser Lys Ala Gly Asp Asp Glu Glu Phe Ser Glu Leu				
970	975	980		
tac acg ttc aag tgg acc acc ctg ctg ata ccc ccg acc acg ctc ctc				3211
Tyr Thr Phe Lys Trp Thr Thr Leu Leu Ile Pro Pro Thr Thr Leu Leu				
985	990	995		
ctg ctg aac ttc atc ggg gtg gtg gcc ggg atc tcg aac gcg atc aac				3259
Leu Leu Asn Phe Ile Gly Val Val Ala Gly Ile Ser Asn Ala Ile Asn				
1000	1005	1010	1015	
aac ggg tac gag tcg tgg ggc ccc ctg ttc ggg aag ctc ttc ttc gcc				3307
Asn Gly Tyr Glu Ser Trp Gly Pro Leu Phe Gly Lys Leu Phe Phe Ala				
1020	1025	1030		

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ttc tgg gtg atc gtc cac ctg tac ccg ttc ctc aag ggt ctg gtg ggg 3355
 Phe Trp Val Ile Val His Leu Tyr Pro Phe Leu Lys Gly Leu Val Gly
 1035 1040 1045

agg cag aac agg acg ccg acg atc gtc atc gtc tgg tcc atc ctg ctg 3403
 Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp Ser Ile Leu Leu
 1050 1055 1060

gcc tcg atc ttc tcg ctc ctg tgg gtc cgc gtc gac ccg ttc ctc gcc 3451
 Ala Ser Ile Phe Ser Leu Leu Trp Val Arg Val Asp Pro Phe Leu Ala
 1065 1070 1075

aag agc aac ggc ccg ctc ctg gag gag tgt ggc ctg gac tgc a 3494
 Lys Ser Asn Gly Pro Leu Leu Glu Glu Cys Gly Leu Asp Cys
 1080 1085 1090

actgaagtgg	ggggccccctg	tcactcgaag	ttctgtcacg	ggcgaattac	gcctgatTTT	3554
ttgttgttgt	tgttgttggA	attctttgtct	gtagatagaa	accacatgtc	cacggcatct	3614
ctgctgtgtc	cattggagca	ggagagaggt	gcctgtgtct	gttttgttag	taaattaaaa	3674
gttttaaagt	tatacagtga	tgcacatTC	agtggccagt	gtattccctt	tttacagtct	3734
gtatatttagc	gacaaaggac	atattggTTA	ggagtttgat	tctttgtaa	aaaaaaaaaa	3794
aaaaaaaaaa	aaaaaaaaaa					3813

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<211> 1094
<212> PRT
<213> Zea mays

<400> 46

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Leu Val Val Ile Arg Arg Asp Arg Glu Ser Gly Ala Ala Gly Gly Gly
      20          25          30
Ala Ala Arg Arg Ala Glu Ala Pro Cys Gln Ile Cys Gly Asp Glu Val
      35          40          45
Gly Val Gly Phe Asp Gly Glu Pro Phe Val Ala Cys Asn Glu Cys Ala
      50          55          60
Phe Pro Val Cys Arg Ala Cys Tyr Glu Tyr Glu Arg Arg Glu Gly Ser
      65          70          75          80
Gln Ala Cys Pro Gln Cys Arg Thr Arg Tyr Lys Arg Leu Lys Gly Cys
      85          90          95
Pro Arg Val Ala Gly Asp Glu Glu Asp Gly Val Asp Asp Leu Glu
      100         105         110
Gly Glu Phe Gly Leu Gln Asp Gly Ala Ala His Glu Asp Asp Pro Gln
      115         120         125
Tyr Val Ala Glu Ser Met Leu Arg Ala Gln Met Ser Tyr Gly Arg Gly
      130         135         140
Gly Asp Ala His Pro Gly Phe Ser Pro Val Pro Asn Val Pro Leu Leu
      145         150         155         160
Thr Asn Gln Gln Met Val Asp Asp Ile Pro Pro Glu Gln His Ala Leu
      165         170         175
Val Pro Ser Tyr Met Ser Gly Gly Gly Gly Lys Arg Ile His
      180         185         190
Pro Leu Pro Phe Ala Asp Pro Asn Leu Pro Val Gln Pro Arg Ser Met
      195         200         205
Asp Pro Ser Lys Asp Leu Ala Ala Tyr Gly Tyr Gly Ser Val Ala Trp
      210         215         220

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Lys Glu Arg Met Glu Gly Trp Lys Gln Lys Glu Arg Leu Gln His
 225 230 235 240
 Val Arg Ser Glu Gly Gly Asp Trp Asp Gly Asp Asp Ala Asp Leu
 245 250 255
 Pro Leu Met Asp Glu Ala Arg Gln Pro Leu Ser Arg Lys Val Pro Ile
 260 265 270
 Ser Ser Ser Arg Ile Asn Pro Tyr Arg Met Ile Ile Val Ile Arg Leu
 275 280 285
 Val Val Leu Gly Phe Phe His Tyr Arg Val Met His Pro Ala Lys
 290 295 300
 Asp Ala Phe Ala Leu Trp Leu Ile Ser Val Ile Cys Glu Ile Trp Phe
 305 310 315 320
 Ala Met Ser Trp Ile Leu Asp Gln Phe Pro Lys Trp Leu Pro Ile Glu
 325 330 335
 Arg Glu Thr Tyr Leu Asp Arg Leu Ser Leu Arg Phe Asp Lys Glu Gly
 340 345 350
 Gln Pro Ser Gln Leu Ala Pro Ile Asp Phe Phe Val Ser Thr Val Asp
 355 360 365
 Pro Thr Lys Glu Pro Pro Leu Val Thr Ala Asn Thr Val Leu Ser Ile
 370 375 380
 Leu Ser Val Asp Tyr Pro Val Glu Lys Val Ser Cys Tyr Val Ser Asp
 385 390 395 400
 Asp Gly Ala Ala Met Leu Thr Phe Glu Ala Leu Ser Glu Thr Ser Glu
 405 410 415
 Phe Ala Lys Lys Trp Val Pro Phe Ser Lys Phe Asn Ile Glu Pro
 420 425 430
 Arg Ala Pro Glu Trp Tyr Phe Gln Gln Lys Ile Asp Tyr Leu Lys Asp
 435 440 445
 Lys Val Ala Ala Ser Phe Val Arg Glu Arg Arg Ala Met Lys Arg Glu
 450 455 460
 Tyr Glu Glu Phe Lys Val Arg Ile Asn Ala Leu Val Ala Lys Ala Gln
 465 470 475 480
 Lys Val Pro Glu Glu Gly Trp Thr Met Gln Asp Gly Ser Pro Trp Pro
 485 490 495
 Gly Asn Asn Val Arg Asp His Pro Gly Met Ile Gln Val Phe Leu Gly
 500 505 510
 Gln Ser Gly Gly Arg Asp Val Glu Gly Asn Glu Leu Pro Arg Leu Val
 515 520 525
 Tyr Val Ser Arg Glu Lys Arg Pro Gly Tyr Asn His His Lys Lys Ala
 530 535 540
 Gly Ala Met Asn Ala Leu Val Arg Val Ser Ala Val Leu Ser Asn Ala
 545 550 555 560
 Ala Tyr Leu Leu Asn Leu Asp Cys Asp His Tyr Ile Asn Asn Ser Lys
 565 570 575
 Ala Ile Lys Glu Ala Met Cys Phe Met Met Asp Pro Leu Val Gly Lys
 580 585 590
 Lys Val Cys Tyr Val Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Lys
 595 600 605
 Asn Asp Arg Tyr Ala Asn Arg Asn Val Val Phe Phe Asp Ile Asn Met
 610 615 620
 Lys Gly Leu Asp Gly Ile Gln Gly Pro Ile Tyr Val Gly Thr Gly Cys
 625 630 635 640
 Val Phe Arg Arg Gln Ala Leu Tyr Gly Tyr Asp Ala Pro Lys Thr Lys
 645 650 655
 Lys Pro Pro Ser Arg Thr Cys Asn Cys Trp Pro Lys Trp Cys Leu Ser
 660 665 670
 Cys Cys Cys Ser Arg Asn Lys Asn Lys Lys Thr Thr Lys Pro Lys
 675 680 685

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Thr Glu Lys Lys Lys Arg Leu Phe Phe Lys Lys Ala Glu Asn Pro Ser
 690 695 700
 Pro Ala Tyr Ala Leu Gly Glu Ile Asp Glu Gly Ala Pro Gly Ala Asp
 705 710 715 720
 Ile Glu Lys Ala Gly Ile Val Asn Gln Gln Lys Leu Glu Lys Lys Phe
 725 730 735
 Gly Gln Ser Ser Val Phe Val Ala Ser Thr Leu Leu Glu Asn Gly Gly
 740 745 750
 Thr Leu Lys Ser Ala Ser Pro Ala Ser Leu Leu Lys Glu Ala Ile His
 755 760 765
 Val Ile Ser Cys Gly Tyr Glu Asp Lys Thr Asp Trp Gly Lys Glu Ile
 770 775 780
 Gly Trp Ile Tyr Gly Ser Ile Thr Glu Asp Ile Leu Thr Gly Phe Lys
 785 790 795 800
 Met His Cys His Gly Trp Arg Ser Ile Tyr Cys Ile Pro Lys Arg Pro
 805 810 815
 Ala Phe Lys Gly Ser Ala Pro Leu Asn Leu Ser Asp Arg Leu His Gln
 820 825 830
 Val Leu Arg Trp Ala Leu Gly Ser Val Glu Ile Phe Phe Ser Lys His
 835 840 845
 Cys Pro Leu Trp Tyr Gly Tyr Gly Gly Leu Lys Phe Leu Glu Arg
 850 855 860
 Phe Ser Tyr Ile Asn Ser Ile Val Tyr Pro Trp Thr Ser Ile Pro Leu
 865 870 875 880
 Leu Ala Tyr Cys Thr Leu Pro Ala Ile Cys Leu Leu Thr Gly Lys Phe
 885 890 895
 Ile Thr Pro Glu Leu Thr Asn Val Ala Ser Ile Trp Phe Met Ala Leu
 900 905 910
 Phe Ile Cys Ile Ser Val Thr Gly Ile Leu Glu Met Arg Trp Ser Gly
 915 920 925
 Val Ala Ile Asp Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly
 930 935 940
 Gly Val Ser Ala His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val
 945 950 955 960
 Phe Ala Gly Ile Asp Thr Ser Phe Thr Val Thr Ser Lys Ala Gly Asp
 965 970 975
 Asp Glu Glu Phe Ser Glu Leu Tyr Thr Phe Lys Trp Thr Thr Leu Leu
 980 985 990
 Ile Pro Pro Thr Thr Leu Leu Leu Asn Phe Ile Gly Val Val Ala
 995 1000 1005
 Gly Ile Ser Asn Ala Ile Asn Asn Gly Tyr Glu Ser Trp Gly Pro Leu
 1010 1015 1020
 Phe Gly Lys Leu Phe Phe Ala Phe Trp Val Ile Val His Leu Tyr Pro
 1025 1030 1035 1040
 Phe Leu Lys Gly Leu Val Gly Arg Gln Asn Arg Thr Pro Thr Ile Val
 1045 1050 1055
 Ile Val Trp Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val
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 Arg Val Asp Pro Phe Leu Ala Lys Ser Asn Gly Pro Leu Leu Glu Glu
 1075 1080 1085
 Cys Gly Leu Asp Cys Asn
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gtcctttct ctcgtccctc ctccccccgt atatgttAAGC cccgccccgc tactactact 180
actagcagca gcagcgctt cgcagcgga gatcggtgt tgatccgtgc cccgctcgga 240
tctcgggact ggtccggct ctgcccaggc cccaggetcc agggcagctc cctcgacgtt 300
tctcggcgag ctcgttgcc atg gag ggc gac gcg gac ggc gtg aag tcg ggg 353
Met Glu Gly Asp Ala Asp Gly Val Lys Ser Gly
1 5 10

agg cgc ggt ggc gga cag gtg tgc cag atc tgc ggc gac ggc gtg ggc 401
Arg Arg Gly Gly Gly Gln Val Cys Gln Ile Cys Gly Asp Gly Val Gly
15 20 25

acc acg gcg gag ggg gac gtc ttc gcc gcc tgc gac gtc tgc ggg ttt 449
Thr Thr Ala Glu Gly Asp Val Phe Ala Ala Cys Asp Val Cys Gly Phe
30 35 40

ccg gtg tgc cgc ccc tgc tac gag tac gag cgc aag gac ggc acg cag 497
Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Asp Gly Thr Gln
45 50 55

gcg tgc ccc cag tgc aag acc aag tac aag cgc cac aag ggg agc ccg 545
Ala Cys Pro Gln Cys Lys Thr Lys Tyr Lys Arg His Lys Gly Ser Pro
60 65 70 75

gcg atc cgt ggg gag gaa gga gac gac act gat gcc gat agc gac ttc 593
Ala Ile Arg Gly Glu Glu Gly Asp Asp Thr Asp Ala Asp Ser Asp Phe
80 85 90

aat tac ctt gca tct ggc aat gag gac cag aag cag aag att gcc gac 641
Asn Tyr Leu Ala Ser Gly Asn Glu Asp Gln Lys Gln Ile Ala Asp
95 100 105

aga atg cgc agc tgg cgc atg aac gtt ggg ggc agc ggg gat gtt ggt 689
Arg Met Arg Ser Trp Arg Met Asn Val Gly Gly Ser Gly Asp Val Gly

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110	115	120	
ccg ccc aag tat gac agt ggc gag atc ggg ctt acc aag tat gac agt Arg Pro Lys Tyr Asp Ser Gly Glu Ile Gly Leu Thr Lys Tyr Asp Ser			737
125	130	135	
ggc gag att cct cggt gga tac atc cca tca gtc act aac agc cag atc Gly Glu Ile Pro Arg Gly Tyr Ile Pro Ser Val Thr Asn Ser Gln Ile			785
140	145	150	155
tca gga gaa atc cct ggt gct tcc cct gac cat cat atg atg tcc cca Ser Gly Glu Ile Pro Gly Ala Ser Pro Asp His His Met Met Ser Pro			833
160	165	170	
act ggg aac att ggc aag cgt gct cca ttt ccc tat gtg aac cat tcg Thr Gly Asn Ile Gly Lys Arg Ala Pro Phe Pro Tyr Val Asn His Ser			881
175	180	185	
cca aat ccg tca agg gag ttc tct ggt agc att ggg aat gtt gcc tgg Pro Asn Pro Ser Arg Glu Phe Ser Gly Ser Ile Gly Asn Val Ala Trp			929
190	195	200	
aaa gag agg gtt gat ggc tgg aaa atg aag cag gac aag ggg acg att Lys Glu Arg Val Asp Gly Trp Lys Met Lys Gln Asp Lys Gly Thr Ile			977
205	210	215	
ccc atg acg aat ggc aca agc att gct ccc tct gag ggt cgg ggt gtt Pro Met Thr Asn Gly Thr Ser Ile Ala Pro Ser Glu Gly Arg Gly Val			1025
220	225	230	235
ggt gat att gat gca tca act gat tac aac atg gaa gat gcc tta ttg Gly Asp Ile Asp Ala Ser Thr Asp Tyr Asn Met Glu Asp Ala Leu Leu			1073
240	245	250	
aac gac gaa act cga cag cct cta tct agg aaa gtt cca ctt cct tcc Asn Asp Glu Thr Arg Gln Pro Leu Ser Arg Lys Val Pro Leu Pro Ser			1121
255	260	265	
tcc agg ata aat cca tac agg atg gtc att gtg ctg cga ttg att gtt Ser Arg Ile Asn Pro Tyr Arg Met Val Ile Val Leu Arg Leu Ile Val			1169
270	275	280	
cta agc atc ttc ttg cac tac cgt atc aca aat cct gtg cgc aat gca Leu Ser Ile Phe Leu His Tyr Arg Ile Thr Asn Pro Val Arg Asn Ala			1217
285	290	295	
tac cca tta tgg ctt cta tct gtt ata tgt gag atc tgg ttt gct ctt Tyr Pro Leu Trp Leu Leu Ser Val Ile Cys Glu Ile Trp Phe Ala Leu			1265
300	305	310	315
tcg tgg ata ttg gat cag ttc cct aag tgg ttt cca atc aac cgg gag Ser Trp Ile Leu Asp Gln Phe Pro Lys Trp Phe Pro Ile Asn Arg Glu			1313
320	325	330	
acg tac ctt gat agg ctg gca tta agg tat gac cgg gaa ggt gag cca Thr Tyr Leu Asp Arg Leu Ala Leu Arg Tyr Asp Arg Glu Gly Glu Pro			1361
335	340	345	

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tct cag ttg gct gtc att ttc gtc agt aca gtc gac cca atg Ser Gln Leu Ala Ala Val Asp Ile Phe Val Ser Thr Val Asp Pro Met	350	355	360	1409
aag gag cct ctt gtc act gcc aat acc gtg cta tcc att ctt gct Lys Glu Pro Pro Leu Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ala	365	370	375	1457
gtg gat tac cct gtg gat aag gtc tct tgc tat gta tct gat gat gga Val Asp Tyr Pro Val Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly				1505
	380	385	390	395
gct gcg atg ctg aca ttt gat gca cta gct gag act tca gag ttt gct Ala Ala Met Leu Thr Phe Asp Ala Leu Ala Glu Thr Ser Glu Phe Ala				1553
	400	405	410	
aga aaa tgg gta cca ttt gtt aag aag tac aac att gaa cct aga gct Arg Lys Trp Val Pro Phe Val Lys Tyr Asn Ile Glu Pro Arg Ala				1601
	415	420	425	
cct gaa tgg tac ttc tcc cag aaa att gat tac ttg aag gac aaa gtc Pro Glu Trp Tyr Phe Ser Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val				1649
	430	435	440	
cac cct tca ttt gtt aaa gac cgc cgg gcc atg aag aga gaa tat gaa His Pro Ser Phe Val Lys Asp Arg Arg Ala Met Lys Arg Glu Tyr Glu				1697
	445	450	455	
gaa ttc aaa gtt agg gta aat ggc ctt gtt gct aag gca cag aaa gtt Glu Phe Lys Val Arg Val Asn Gly Leu Val Ala Lys Ala Gln Lys Val				1745
	460	465	470	475
cct gag gaa gga tgg atc atg caa gat ggc aca cca tgg cca gga aac Pro Glu Glu Gly Trp Ile Met Gln Asp Gly Thr Pro Trp Pro Gly Asn				1793
	480	485	490	
aat acc mgg gac cat cct gga atg att cag gtt ttc ctt ggt cac agt Asn Thr Xaa Asp His Pro Gly Met Ile Gln Val Phe Leu Gly His Ser				1841
	495	500	505	
ggc ctt gat act gag ggc aat gag cta ccc cgt ttg gtc tat gtt Gly Gly Leu Asp Thr Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val				1889
	510	515	520	
tct cgt gaa aag cgt cct gga ttc cag cat cac aag aaa gct ggt gcc Ser Arg Glu Lys Arg Pro Gly Phe Gln His His Lys Lys Ala Gly Ala				1937
	525	530	535	
atg aat gct ctt gtt cgt gtc tca gct gtg ctt acc aat gga caa tac Met Asn Ala Leu Val Arg Val Ser Ala Val Leu Thr Asn Gly Gln Tyr				1985
	540	545	550	555
atg ttg aat ctt gat tgt gat cac tac att aac aac agt aag gct ctc Met Leu Asn Leu Asp Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Leu				2033
	560	565	570	
agg gaa gct atg tgc ttc ctt atg gac cct aac cta gga agg agt gtc Arg Glu Ala Met Cys Phe Leu Met Asp Pro Asn Leu Gly Arg Ser Val				2081

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575

580

585

tgc tac gtc cag ttt ccc cag aga ttc gat ggc att gac agg aat gat Cys Tyr Val Gln Phe Pro Gln Arg Phe Asp Gly Ile Asp Arg Asn Asp 590 595 600		2129
cga tat gcc aac agg aac acc gtg ttt ttc gat att aac ttg aga ggt Arg Tyr Ala Asn Arg Asn Thr Val Phe Phe Asp Ile Asn Leu Arg Gly 605 610 615		2177
ctt gat ggc atc caa gga cca gtt tat gtc gga act ggc tgt gtt ttc Leu Asp Gly Ile Gln Gly Pro Val Tyr Val Gly Thr Gly Cys Val Phe 620 625 630 635		2225
aac cga aca gct cta tat ggt tat gag ccc cca att aag cag aag aag Asn Arg Thr Ala Leu Tyr Gly Tyr Glu Pro Pro Ile Lys Gln Lys Lys 640 645 650		2273
ggg ggt ttc ttg tca tca cta tgt ggc ggt agg aag aag gca agc aaa Gly Gly Phe Leu Ser Ser Leu Cys Gly Gly Arg Lys Lys Ala Ser Lys 655 660 665		2321
tca aag aag ggc tcg gac aag aag tcg cag aag cat gtg gac agt Ser Lys Lys Gly Ser Asp Lys Lys Ser Gln Lys His Val Asp Ser 670 675 680		2369
tct gtg cca gta ttc aac ctt gaa gat ata gag gag gga gtt gaa ggc Ser Val Pro Val Phe Asn Leu Glu Asp Ile Glu Glu Gly Val Glu Gly 685 690 695		2417
gct gga ttt gac gac gag aaa tca ctt ctt atg tct caa atg agc ctg Ala Gly Phe Asp Asp Glu Lys Ser Leu Leu Met Ser Gln Met Ser Leu 700 705 710 715		2465
gag aag aga ttt ggc cag tcc gca gcg ttt gtt gcc tcc act ctg atg Glu Lys Arg Phe Gly Gln Ser Ala Ala Phe Val Ala Ser Thr Leu Met 720 725 730		2513
gag tat ggt ggt gtt cct cag tcc gca act ccg gag tct ctt ctg aaa Glu Tyr Gly Val Pro Gln Ser Ala Thr Pro Glu Ser Leu Leu Lys 735 740 745		2561
gaa gct atc cat gtt ata agc tgt ggc tat gag gac aag act gaa tgg Glu Ala Ile His Val Ile Ser Cys Gly Tyr Glu Asp Lys Thr Glu Trp 750 755 760		2609
gga act gag atc ggg tgg atc tac ggt tct gtg aca gaa gac att ctc Gly Thr Glu Ile Gly Trp Ile Tyr Gly Ser Val Thr Glu Asp Ile Leu 765 770 775		2657
acc gga ttc aag atg cac gcg cga ggc tgg cgg tcg atc tac tgc atg Thr Gly Phe Lys Met His Ala Arg Gly Trp Arg Ser Ile Tyr Cys Met 780 785 790 795		2705
ccc aag cgg cca gct ttc aag ggg tct gcc ccc atc aat ctt tcg gac Pro Lys Arg Pro Ala Phe Lys Gly Ser Ala Pro Ile Asn Leu Ser Asp 800 805 810		2753

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cgt ctg aac cag gtg ctc cgg tgg gct ctt ggg tcc gtg gag atc ctc Arg Leu Asn Gln Val Leu Arg Trp Ala Leu Gly Ser Val Glu Ile Leu 815 820 825	2801
ttc agc cgg cac tgc ccc ctg tgg tac ggc tac gga ggg cgg ctc aag Phe Ser Arg His Cys Pro Leu Trp Tyr Gly Tyr Gly Arg Leu Lys 830 835 840	2849
ttc ctg gag aga ttc gcg tac atc aac acc acc atc tac ccg ctc acg Phe Leu Glu Arg Phe Ala Tyr Ile Asn Thr Thr Ile Tyr Pro Leu Thr 845 850 855	2897
tcc atc ccg ctt ctc atc tac tgc atc ctg ccc gcc atc tgt ctg ctc Ser Ile Pro Leu Leu Ile Tyr Cys Ile Leu Pro Ala Ile Cys Leu Leu 860 865 870 875	2945
acc gga aag ttc atc att cca gag atc agc aac ttc gcc agc atc tgg Thr Gly Lys Phe Ile Ile Pro Glu Ile Ser Asn Phe Ala Ser Ile Trp 880 885 890	2993
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agg tgg agc ggg gtg ggc atc gac gag tgg tgg agg aac gag cag ttc Arg Trp Ser Gly Val Gly Ile Asp Glu Trp Trp Arg Asn Glu Gln Phe 910 915 920	3089
tgg gtg atc ggg ggc atc tcc gcg cac ctc ttc gcc gtg ttc cag ggc Trp Val Ile Gly Gly Ile Ser Ala His Leu Phe Ala Val Phe Gln Gly 925 930 935	3137
ctg ctc aag gtg ctg gcc ggc atc gac acc aac ttc acc gtc acc tcc Leu Leu Lys Val Leu Ala Gly Ile Asp Thr Asn Phe Thr Val Thr Ser 940 945 950 955	3185
aag gcc tcg gac gag gac ggc gac ttc gcg gag ctg tac atg ttc aag Lys Ala Ser Asp Glu Asp Gly Asp Phe Ala Glu Leu Tyr Met Phe Lys 960 965 970	3233
tgg acg acg ctc ctg atc ccg ccc acc acc atc ctg atc atc aac ctg Trp Thr Thr Leu Leu Ile Pro Pro Thr Thr Ile Leu Ile Ile Asn Leu 975 980 985	3281
gtc ggc gtc gcc ggc atc tcc tac gcc atc aac agc gga tac cag Val Gly Val Val Ala Gly Ile Ser Tyr Ala Ile Asn Ser Gly Tyr Gln 990 995 1000	3329
tcg tgg ggc ccg ctc ttc ggc aag ctc ttc ttc gcc ttc tgg gtc atc Ser Trp Gly Pro Leu Phe Gly Lys Leu Phe Phe Ala Phe Trp Val Ile 1005 1010 1015	3377
gtc cac ctg tac ccg ttc ctc aag ggc ctc atg ggc agg cag aac cgc Val His Leu Tyr Pro Phe Leu Lys Gly Leu Met Gly Arg Gln Asn Arg 1020 1025 1030 1035	3425
acc ccg acc atc gtc gtc tgg gccatcctgc tggcgatccat cttctccatttg Thr Pro Thr Ile Val Val Val Trp	3479

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1040

ctgtggggtc	gcatcgaccc	cttcaccacc	cgcgtcaactg	gcccgatatac	ccagacgtgt	3539
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gcccattcttt	gtctgttaag	ttatatatatata	ataagcagca	agtggcgta	tttacagcta	3659
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<400> 50

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Gln	Val	Cys	Gln	Ile	Cys	Gly	Asp	Gly	Val	Gly	Thr	Thr	Ala	Glu	Gly
								20		25			30		
Asp	Val	Phe	Ala	Ala	Cys	Asp	Val	Cys	Gly	Phe	Pro	Val	Cys	Arg	Pro
								35		40			45		
Cys	Tyr	Glu	Tyr	Glu	Arg	Lys	Asp	Gly	Thr	Gln	Ala	Cys	Pro	Gln	Cys
						50		55			60				
Lys	Thr	Lys	Tyr	Lys	Arg	His	Lys	Gly	Ser	Pro	Ala	Ile	Arg	Gly	Glu
						65		70			75		80		
Glu	Gly	Asp	Asp	Thr	Asp	Ala	Asp	Ser	Asp	Phe	Asn	Tyr	Leu	Ala	Ser
						85			90			95			
Gly	Asn	Glu	Asp	Gln	Lys	Gln	Lys	Ile	Ala	Asp	Arg	Met	Arg	Ser	Trp
						100			105			110			
Arg	Met	Asn	Val	Gly	Gly	Ser	Gly	Asp	Val	Gly	Arg	Pro	Lys	Tyr	Asp
						115			120			125			
Ser	Gly	Glu	Ile	Gly	Leu	Thr	Lys	Tyr	Asp	Ser	Gly	Glu	Ile	Pro	Arg
						130			135			140			
Gly	Tyr	Ile	Pro	Ser	Val	Thr	Asn	Ser	Gln	Ile	Ser	Gly	Glu	Ile	Pro
						145			150			155			160
Gly	Ala	Ser	Pro	Asp	His	His	Met	Met	Ser	Pro	Thr	Gly	Asn	Ile	Gly
						165			170			175			
Lys	Arg	Ala	Pro	Phe	Pro	Tyr	Val	Asn	His	Ser	Pro	Asn	Pro	Ser	Arg
						180			185			190			
Glu	Phe	Ser	Gly	Ser	Ile	Gly	Asn	Val	Ala	Trp	Lys	Glu	Arg	Val	Asp
						195			200			205			
Gly	Trp	Lys	Met	Lys	Gln	Asp	Lys	Gly	Thr	Ile	Pro	Met	Thr	Asn	Gly
						210			215			220			
Thr	Ser	Ile	Ala	Pro	Ser	Glu	Gly	Arg	Gly	Val	Gly	Asp	Ile	Asp	Ala
						225			230			235			240
Ser	Thr	Asp	Tyr	Asn	Met	Glu	Asp	Ala	Leu	Leu	Asn	Glu	Thr	Arg	
						245			250			255			
Gln	Pro	Leu	Ser	Arg	Lys	Val	Pro	Leu	Pro	Ser	Ser	Arg	Ile	Asn	Pro
						260			265			270			
Tyr	Arg	Met	Val	Ile	Val	Leu	Arg	Leu	Ile	Val	Leu	Ser	Ile	Phe	Leu
						275			280			285			
His	Tyr	Arg	Ile	Thr	Asn	Pro	Val	Arg	Asn	Ala	Tyr	Pro	Leu	Trp	Leu
						290			295			300			
Leu	Ser	Val	Ile	Cys	Glu	Ile	Trp	Phe	Ala	Leu	Ser	Trp	Ile	Leu	Asp
						305			310			315			320
Gln	Phe	Pro	Lys	Trp	Phe	Pro	Ile	Asn	Arg	Glu	Thr	Tyr	Leu	Asp	Arg
						325			330			335			
Leu	Ala	Leu	Arg	Tyr	Asp	Arg	Glu	Gly	Glu	Pro	Ser	Gln	Leu	Ala	Ala
						340			345			350			

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Val Asp Ile Phe Val Ser Thr Val Asp Pro Met Lys Glu Pro Pro Leu
 355 360 365
 Val Thr Ala Asn Thr Val Leu Ser Ile Leu Ala Val Asp Tyr Pro Val
 370 375 380
 Asp Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ala Ala Met Leu Thr
 385 390 395 400
 Phe Asp Ala Leu Ala Glu Thr Ser Glu Phe Ala Arg Lys Trp Val Pro
 405 410 415
 Phe Val Lys Lys Tyr Asn Ile Glu Pro Arg Ala Pro Glu Trp Tyr Phe
 420 425 430
 Ser Gln Lys Ile Asp Tyr Leu Lys Asp Lys Val His Pro Ser Phe Val
 435 440 445
 Lys Asp Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg
 450 455 460
 Val Asn Gly Leu Val Ala Lys Ala Gln Lys Val Pro Glu Glu Gly Trp
 465 470 475 480
 Ile Met Gln Asp Gly Thr Pro Trp Pro Gly Asn Asn Thr Xaa Asp His
 485 490 495
 Pro Gly Met Ile Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr
 500 505 510
 Glu Gly Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg
 515 520 525
 Pro Gly Phe Gln His His Lys Lys Ala Gly Ala Met Asn Ala Leu Val
 530 535 540
 Arg Val Ser Ala Val Leu Thr Asn Gly Gln Tyr Met Leu Asn Leu Asp
 545 550 555 560
 Cys Asp His Tyr Ile Asn Asn Ser Lys Ala Leu Arg Glu Ala Met Cys
 565 570 575
 Phe Leu Met Asp Pro Asn Leu Gly Arg Ser Val Cys Tyr Val Gln Phe
 580 585 590
 Pro Gln Arg Phe Asp Gly Ile Asp Arg Asn Asp Arg Tyr Ala Asn Arg
 595 600 605
 Asn Thr Val Phe Phe Asp Ile Asn Leu Arg Gly Leu Asp Gly Ile Gln
 610 615 620
 Gly Pro Val Tyr Val Gly Thr Gly Cys Val Phe Asn Arg Thr Ala Leu
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 Tyr Gly Tyr Glu Pro Pro Ile Lys Gln Lys Lys Gly Gly Phe Leu Ser
 645 650 655
 Ser Leu Cys Gly Gly Arg Lys Lys Ala Ser Lys Ser Lys Lys Gly Ser
 660 665 670
 Asp Lys Lys Ser Gln Lys His Val Asp Ser Ser Val Pro Val Phe
 675 680 685
 Asn Leu Glu Asp Ile Glu Glu Gly Val Glu Gly Ala Gly Phe Asp Asp
 690 695 700
 Glu Lys Ser Leu Leu Met Ser Gln Met Ser Leu Glu Lys Arg Phe Gly
 705 710 715 720
 Gln Ser Ala Ala Phe Val Ala Ser Thr Leu Met Glu Tyr Gly Val
 725 730 735
 Pro Gln Ser Ala Thr Pro Glu Ser Leu Leu Lys Glu Ala Ile His Val
 740 745 750
 Ile Ser Cys Gly Tyr Glu Asp Lys Thr Glu Trp Gly Thr Glu Ile Gly
 755 760 765
 Trp Ile Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met
 770 775 780
 His Ala Arg Gly Trp Arg Ser Ile Tyr Cys Met Pro Lys Arg Pro Ala
 785 790 795 800
 Phe Lys Gly Ser Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val
 805 810 815

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Leu Arg Trp Ala Leu Gly Ser Val Glu Ile Leu Phe Ser Arg His Cys
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 Pro Leu Trp Tyr Gly Tyr Gly Arg Leu Lys Phe Leu Glu Arg Phe
 835 840 845
 Ala Tyr Ile Asn Thr Thr Ile Tyr Pro Leu Thr Ser Ile Pro Leu Leu
 850 855 860
 Ile Tyr Cys Ile Leu Pro Ala Ile Cys Leu Leu Thr Gly Lys Phe Ile
 865 870 875 880
 Ile Pro Glu Ile Ser Asn Phe Ala Ser Ile Trp Phe Ile Ser Leu Phe
 885 890 895
 Ile Ser Ile Phe Ala Thr Gly Ile Leu Glu Met Arg Trp Ser Gly Val
 900 905 910
 Gly Ile Asp Glu Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly
 915 920 925
 Ile Ser Ala His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu
 930 935 940
 Ala Gly Ile Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu
 945 950 955 960
 Asp Gly Asp Phe Ala Glu Leu Tyr Met Phe Lys Trp Thr Thr Leu Leu
 965 970 975
 Ile Pro Pro Thr Thr Ile Leu Ile Ile Asn Leu Val Gly Val Val Ala
 980 985 990
 Gly Ile Ser Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu
 995 1000 1005
 Phe Gly Lys Leu Phe Phe Ala Phe Trp Val Ile Val His Leu Tyr Pro
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 Phe Leu Lys Gly Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val
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 Val Val Trp

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gtcggtttg gtgtcggttg cgtgtggagc cgtctcggtg ggagcagcgg ggagggagcg	180
gag atg gcg gcc aac aag ggg atg gtg gcg ggc tcg cac aac cgc aac	228
Met Ala Ala Asn Lys Gly Met Val Ala Gly Ser His Asn Arg Asn	
1 5 10 15	
gag ttc gtc atg atc cgc cac gac ggc gat gtg ccg ggc tcg gct aag	276
Glu Phe Val Met Ile Arg His Asp Gly Asp Val Pro Gly Ser Ala Lys	
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ccc aca aag agt gcg aat gga cag gtc tgc cag att tgc ggt gac tct	324
Pro Thr Lys Ser Ala Asn Gly Gln Val Cys Gln Ile Cys Gly Asp Ser	
35 40 45	
gtg ggt gtt tca gcc act ggt gat gtc ttt gtt gcc tgc aat gag tgt	372
Val Gly Val Ser Ala Thr Gly Asp Val Phe Val Ala Cys Asn Glu Cys	
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gcc ttc cct gtc tgc cgc cca tgc tat gag tat gag cgc aag gag ggg	420
Ala Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Glu Gly	
65 70 75	
aac caa tgc tgc ccc cag tgc aag act aga tac aag aga cag aaa ggt	468
Asn Gln Cys Cys Pro Gln Cys Lys Thr Arg Tyr Lys Arg Gln Lys Gly	
80 85 90 95	
agc cct cga gtt cat ggt gat gag gat gaa gat gtt gat gac cta	516
Ser Pro Arg Val His Gly Asp Glu Asp Glu Asp Val Asp Asp Leu	
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gac aat gaa ttc aac tac aag caa ggc agt ggg aaa ggc cca gag tgg	564
Asp Asn Glu Phe Asn Tyr Lys Gln Gly Ser Gly Lys Gly Pro Glu Trp	
115 120 125	
caa ctg caa gga gat gat gct gat ctg tct tca tct gct cgc cat gag	612
Gln Leu Gln Gly Asp Asp Ala Asp Leu Ser Ser Ser Ala Arg His Glu	
130 135 140	
cca cat cat cgg att cca cgc ctg aca agc ggt caa cag ata tct gga	660
Pro His His Arg Ile Pro Arg Leu Thr Ser Gly Gln Gln Ile Ser Gly	
145 150 155	
gag att cct gat gct tcc cct gac cgt cat tct atc cgc agt cca aca	708
Glu Ile Pro Asp Ala Ser Pro Asp Arg His Ser Ile Arg Ser Pro Thr	
160 165 170 175	
tcg agc tat gtt gat cca agc gtc cca gtt cct gtg agg att gtg gac	756
Ser Ser Tyr Val Asp Pro Ser Val Pro Val Pro Val Arg Ile Val Asp	
180 185 190	
ccc tcg aag gac ttg aat tcc tat ggg ctt aat agt gtt gac tgg aag	804
Pro Ser Lys Asp Leu Asn Ser Tyr Gly Leu Asn Ser Val Asp Trp Lys	
195 200 205	
gaa aga gtt gag agc tgg agg gtt aaa cag gac aaa aat atg atg caa	852
Glu Arg Val Glu Ser Trp Arg Val Lys Gln Asp Lys Asn Met Met Gln	

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210

215

220

gtg act aat aaa tat cca gag gct aga gga gga gac atg gag ggg act Val Thr Asn Lys Tyr Pro Glu Ala Arg Gly Gly Asp Met Glu Gly Thr 225	230	235	900	
ggc tca aat gga gaa nat atg caa atg gtt gat gat gca cgg cta cct Gly Ser Asn Gly Glu Xaa Met Gln Met Val Asp Asp Ala Arg Leu Pro 240	245	250	948	
ttg agc cgt atc gtg cca att tcc tca aac cag ctc aac ctt tac cgg Leu Ser Arg Ile Val Pro Ile Ser Ser Asn Gln Leu Asn Leu Tyr Arg 260	265	270	996	
gta gtg atc att ctc cgt ctt atc ctg tgc ttc ttc cag tat Val Val Ile Ile Leu Arg Leu Ile Leu Cys Phe Phe Gln Tyr 275	280	285	1044	
cgt gtc agt cat cca gtg cgt gat gct tat gga tta tgg cta gta tct Arg Val Ser His Pro Val Arg Asp Ala Tyr Gly Leu Trp Leu Val Ser 290	295	300	1092	
gtt atc tgc gag gtc tgg ttt gcc ttg tct tgg ctt cta gat cag ttc Val Ile Cys Glu Val Trp Phe Ala Leu Ser Trp Leu Leu Asp Gln Phe 305	310	315	1140	
cca aaa tgg tat cca atc aac cgt gag aca tat ctt gac agg ctt gca Pro Lys Trp Tyr Pro Ile Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala 320	325	330	335	1188
ttg agg tat gat aga gag gga gag cca tca cag ctg gct ccc att gat Leu Arg Tyr Asp Arg Glu Gly Glu Pro Ser Gln Leu Ala Pro Ile Asp 340	345	350	1236	
gtc ttc gtc agt aca gtg gat cca ttg aag gaa cct cca ctg atc aca Val Phe Val Ser Thr Val Asp Pro Leu Lys Glu Pro Pro Leu Ile Thr 355	360	365	1284	
gcc aac act gtt ttg tcc att ctt tct gtg gat tac cct gtt gac aaa Ala Asn Thr Val Leu Ser Ile Leu Ser Val Asp Tyr Pro Val Asp Lys 370	375	380	1332	
gtg tca tgc tat gtt tct gat gat ggt tca gct atg ctg act ttt gag Val Ser Cys Tyr Val Ser Asp Asp Gly Ser Ala Met Leu Thr Phe Glu 385	390	395	1380	
tct ctc tca gaa acc gca gaa ttt gct aga aag tgg gtt ccc ttt tgt Ser Leu Ser Glu Thr Ala Glu Phe Ala Arg Lys Trp Val Pro Phe Cys 400	405	410	415	1428
aag aag cac aat att gaa cca aga gct cca gaa ttt tac ttt gct caa Lys Lys His Asn Ile Glu Pro Arg Ala Pro Glu Phe Tyr Phe Ala Gln 420	425	430	1476	
aaa ata gat tac ctg aag gac aaa att caa cct tca ttt gtt aag gaa Lys Ile Asp Tyr Leu Lys Asp Lys Ile Gln Pro Ser Phe Val Lys Glu 435	440	445	1524	

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aga cgc gca atg aag agg gag tat gaa gaa ttc aaa gta aga atc aat Arg Arg Ala Met Lys Arg Glu Tyr Glu Glu Phe Lys Val Arg Ile Asn 450 455 460	1572
gcc ctt gtt gcc aaa gca cag aaa gtg cct gaa gag ggg tgg acc atg Ala Leu Val Ala Lys Ala Gln Lys Val Pro Glu Gly Trp Thr Met 465 470 475	1620
gct gat gga act gca tgg cct ggg aat aat cct agg gac cat cct ggc Ala Asp Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly 480 485 490 495	1668
atg att cag gtt ttc ttg ggg cac agt ggt ggg ctc gac act gat gga Met Ile Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly 500 505 510	1716
aat gag tta cca cgt ctt gtc tat gtc tct cgt gaa aag aga cca ggc Asn Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly 515 520 525	1764
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tct gct gtg ctg aca aat ggt gcc tat ctt ctc aat gtg gat tgc gac Ser Ala Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp 545 550 555	1860
cat tac ttc aat agc agc aaa gct ctt aga gaa gca atg tgc ttc atg His Tyr Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met 560 565 570 575	1908
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aga ttt gat ggc att gac ttg cac gat cga tat gct aat cgg aac ata Arg Phe Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile 595 600 605	2004
gtt ttc ttt gat atc aac atg aaa ggt ctg gat ggc att cag ggt cca Val Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro 610 615 620	2052
gtt tac gtg gga aca gga tgc tgt ttc aat aga cag gct ttg tat gga Val Tyr Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly 625 630 635	2100
tac gat cct gtt ttg act gaa gct gat ctg gag cca aac att gtt att Tyr Asp Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Ile 640 645 650 655	2148
aag agc tgc tgt ggt aga agg aag aaa aag aac aag agt tat atg gat Lys Ser Cys Cys Gly Arg Arg Lys Lys Asn Lys Ser Tyr Met Asp 660 665 670	2196
agt caa agc cgt att atg aag aga aca gaa tct tca gct ccc atc ttc Ser Gln Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe	2244

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675

680

685

aat atg gaa gac atc gaa gag ggt att gaa ggt tac gag gat gaa agg Asn Met Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg 690 695 700	2292
tca gtg ctt atg tcc cag agg aaa ttg gag aaa cgc ttt ggt cag tct Ser Val Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser 705 710 715	2340
cct att ttc att gca tcc acc ttt atg aca caa ggt ggc ata cca cct Pro Ile Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro 720 725 730 735	2388
tca aca aac cca gct tct cta cta aag gaa gct atc cat gtc atc agt Ser Thr Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser 740 745 750	2436
tgt gga tat gag gac aaa act gaa tgg gga aaa gag att ggc tgg atc Cys Gly Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile 755 760 765	2484
tat ggt tca gta acg gag gat att ctg act ggg ttt aaa atg cat gca Tyr Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala 770 775 780	2532
agg ggc tgg caa tca atc tac tgc atg cca cca cga cct tgt ttc aag Arg Gly Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys 785 790 795	2580
ggc tct gca cca atc aat ctt tcc gat cgt ctt aat cag gtg ctc cgt Gly Ser Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg 800 805 810 815	2628
tgg gct ctt ggg tca gtg gaa att ctg ctt agt aga cat tgt cct atc Trp Ala Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile 820 825 830	2676
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atc aac act att gta tat cca atc aca tcc att ccg ctt att gcc tat Ile Asn Thr Ile Val Tyr Pro Ile Thr Ser Ile Pro Leu Ile Ala Tyr 850 855 860	2772
tgt gtg ctt ccc gct atc tgc ctc ctt acc aat aaa ttt atc att cct Cys Val Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro 865 870 875	2820
gag att agc aat tat gct ggg atg ttc ttc att ctt ctt ttc gcc tcc Glu Ile Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser 880 885 890 895	2868
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gaa gat tgg tgg aga aat gag cag ttt tgg gtt att ggt ggc acc tct Glu Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser 915 920 925	2964
gcc cat ctc ttc gca gtg ttc cag ggt ctg ctg aaa gtg ttg gct ggg Ala His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly 930 935 940	3012
att gat acc aac ttc aca gtt acc tca aag gca tct gat gag gat ggc Ile Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly 945 950 955	3060
gac ttt gct gag cta tat gtg ttc aag tgg acc agt ttg ctc att cct Asp Phe Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro 960 965 970 975	3108
ccg acc act gtt ctt gtc att aac ctg gtc gga atg gtg gca gga att Pro Thr Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile 980 985 990	3156
tct tat gcc att aac agt ggc tac caa tcc tgg ggt ccg ctc ttt gga Ser Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly 995 1000 1005	3204
aag ctg ttc ttc tcg atc tgg gtg atc ctc cat ctc tac ccc ttc ctc Lys Leu Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu 1010 1015 1020	3252
aag ggt ctc atg gga agg cag aac cgc aca cca aca atc gtc att gtc Lys Gly Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val 1025 1030 1035	3300
tgg tcc atc ctt ctt gca tct atc ttc tcc ttg ctg tgg gtg aag atc Trp Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile 1040 1045 1050 1055	3348
gat cct ttc atc tcc ccg aca cag aaa gct gct gcc ttg ggg caa tgt Asp Pro Phe Ile Ser Pro Thr Gln Lys Ala Ala Ala Leu Gly Gln Cys 1060 1065 1070	3396
ggc gtc aac t gctgatcgag acagtgactc ttatttgaag aggctcaatc Gly Val Asn	3446
 aagatctgcc ccctcggtta aataacctgag gaggttagat gggaaattctt tttgtttag gtgaggatgg atttgcattt aagtttatgcc tctgttcatc agcttcttcc gtgcgggtgc tgctcggtac taagaatcac ggagccttcc taccttccat gtatcgccag ccagcagcgt aagatgtgaa ttttgaagtt ttgttatgcg tgcatgtt ttttttagag taaaattatca tttgtttgtg ggaactgttc acacgagctt ataatggcaa tgctgttatt taaaaaaaaa aaaaaaaaa	3506 3566 3626 3686 3746 3753
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			20						25					30	
Thr	Lys	Ser	Ala	Asn	Gly	Gln	Val	Cys	Gln	Ile	Cys	Gly	Asp	Ser	Val
			35					40					45		
Gly	Val	Ser	Ala	Thr	Gly	Asp	Val	Phe	Val	Ala	Cys	Asn	Glu	Cys	Ala
			50					55					60		
Phe	Pro	Val	Cys	Arg	Pro	Cys	Tyr	Glu	Tyr	Glu	Arg	Lys	Glu	Gly	Asn
	65						70			75			80		
Gln	Cys	Cys	Pro	Gln	Cys	Lys	Thr	Arg	Tyr	Lys	Arg	Gln	Lys	Gly	Ser
	85						90			95					
Pro	Arg	Val	His	Gly	Asp	Glu	Asp	Glu	Asp	Val	Asp	Asp	Leu	Asp	
	100						105					110			
Asn	Glu	Phe	Asn	Tyr	Lys	Gln	Gly	Ser	Gly	Lys	Gly	Pro	Glu	Trp	Gln
	115						120					125			
Leu	Gln	Gly	Asp	Asp	Ala	Asp	Leu	Ser	Ser	Ser	Ala	Arg	His	Glu	Pro
	130						135					140			
His	His	Arg	Ile	Pro	Arg	Leu	Thr	Ser	Gly	Gln	Gln	Ile	Ser	Gly	Glu
	145						150			155			160		
Ile	Pro	Asp	Ala	Ser	Pro	Asp	Arg	His	Ser	Ile	Arg	Ser	Pro	Thr	Ser
	165						170					175			
Ser	Tyr	Val	Asp	Pro	Ser	Val	Pro	Val	Pro	Val	Arg	Ile	Val	Asp	Pro
	180						185					190			
Ser	Lys	Asp	Leu	Asn	Ser	Tyr	Gly	Leu	Asn	Ser	Val	Asp	Trp	Lys	Glu
	195						200					205			
Arg	Val	Glu	Ser	Trp	Arg	Val	Lys	Gln	Asp	Lys	Asn	Met	Met	Gln	Val
	210						215					220			
Thr	Asn	Lys	Tyr	Pro	Glu	Ala	Arg	Gly	Gly	Asp	Met	Glu	Gly	Thr	Gly
	225						230					235			240
Ser	Asn	Gly	Glu	Xaa	Met	Gln	Met	Val	Asp	Asp	Ala	Arg	Leu	Pro	Leu
	245						250					255			
Ser	Arg	Ile	Val	Pro	Ile	Ser	Ser	Asn	Gln	Leu	Asn	Leu	Tyr	Arg	Val
	260						265					270			
Val	Ile	Ile	Leu	Arg	Leu	Ile	Ile	Leu	Cys	Phe	Phe	Phe	Gln	Tyr	Arg
	275						280					285			
Val	Ser	His	Pro	Val	Arg	Asp	Ala	Tyr	Gly	Leu	Trp	Leu	Val	Ser	Val
	290						295					300			
Ile	Cys	Glu	Val	Trp	Phe	Ala	Leu	Ser	Trp	Leu	Leu	Asp	Gln	Phe	Pro
	305						310					315			320
Lys	Trp	Tyr	Pro	Ile	Asn	Arg	Glu	Thr	Tyr	Leu	Asp	Arg	Leu	Ala	Leu
	325						330					335			
Arg	Tyr	Asp	Arg	Glu	Gly	Glu	Pro	Ser	Gln	Leu	Ala	Pro	Ile	Asp	Val
	340						345					350			
Phe	Val	Ser	Thr	Val	Asp	Pro	Leu	Lys	Glu	Pro	Pro	Leu	Ile	Thr	Ala
	355						360					365			
Asn	Thr	Val	Leu	Ser	Ile	Leu	Ser	Val	Asp	Tyr	Pro	Val	Asp	Lys	Val
	370						375					380			
Ser	Cys	Tyr	Val	Ser	Asp	Asp	Gly	Ser	Ala	Met	Leu	Thr	Phe	Glu	Ser
	385						390					395			400
Leu	Ser	Glu	Thr	Ala	Glu	Phe	Ala	Arg	Lys	Trp	Val	Pro	Phe	Cys	Lys
	405						410					415			
Lys	His	Asn	Ile	Glu	Pro	Arg	Ala	Pro	Glu	Phe	Tyr	Phe	Ala	Gln	Lys
	420						425					430			
Ile	Asp	Tyr	Leu	Lys	Asp	Lys	Ile	Gln	Pro	Ser	Phe	Val	Lys	Glu	Arg
	435						440					445			
Arg	Ala	Met	Lys	Arg	Glu	Tyr	Glu	Glu	Phe	Lys	Val	Arg	Ile	Asn	Ala
	450						455					460			
Leu	Val	Ala	Lys	Ala	Gln	Lys	Val	Pro	Glu	Glu	Gly	Trp	Thr	Met	Ala

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465	470	475	480
Asp Gly Thr Ala Trp Pro Gly Asn Asn Pro Arg Asp His Pro Gly Met			
485	490	495	
Ile Gln Val Phe Leu Gly His Ser Gly Gly Leu Asp Thr Asp Gly Asn			
500	505	510	
Glu Leu Pro Arg Leu Val Tyr Val Ser Arg Glu Lys Arg Pro Gly Phe			
515	520	525	
Gln His His Lys Lys Ala Gly Ala Met Asn Ala Leu Ile Arg Val Ser			
530	535	540	
Ala Val Leu Thr Asn Gly Ala Tyr Leu Leu Asn Val Asp Cys Asp His			
545	550	555	560
Tyr Phe Asn Ser Ser Lys Ala Leu Arg Glu Ala Met Cys Phe Met Met			
565	570	575	
Asp Pro Ala Leu Gly Arg Lys Thr Cys Tyr Val Gln Phe Pro Gln Arg			
580	585	590	
Phe Asp Gly Ile Asp Leu His Asp Arg Tyr Ala Asn Arg Asn Ile Val			
595	600	605	
Phe Phe Asp Ile Asn Met Lys Gly Leu Asp Gly Ile Gln Gly Pro Val			
610	615	620	
Tyr Val Gly Thr Gly Cys Cys Phe Asn Arg Gln Ala Leu Tyr Gly Tyr			
625	630	635	640
Asp Pro Val Leu Thr Glu Ala Asp Leu Glu Pro Asn Ile Val Ile Lys			
645	650	655	
Ser Cys Cys Gly Arg Arg Lys Lys Lys Asn Lys Ser Tyr Met Asp Ser			
660	665	670	
Gln Ser Arg Ile Met Lys Arg Thr Glu Ser Ser Ala Pro Ile Phe Asn			
675	680	685	
Met Glu Asp Ile Glu Glu Gly Ile Glu Gly Tyr Glu Asp Glu Arg Ser			
690	695	700	
Val Leu Met Ser Gln Arg Lys Leu Glu Lys Arg Phe Gly Gln Ser Pro			
705	710	715	720
Ile Phe Ile Ala Ser Thr Phe Met Thr Gln Gly Gly Ile Pro Pro Ser			
725	730	735	
Thr Asn Pro Ala Ser Leu Leu Lys Glu Ala Ile His Val Ile Ser Cys			
740	745	750	
Gly Tyr Glu Asp Lys Thr Glu Trp Gly Lys Glu Ile Gly Trp Ile Tyr			
755	760	765	
Gly Ser Val Thr Glu Asp Ile Leu Thr Gly Phe Lys Met His Ala Arg			
770	775	780	
Gly Trp Gln Ser Ile Tyr Cys Met Pro Pro Arg Pro Cys Phe Lys Gly			
785	790	795	800
Ser Ala Pro Ile Asn Leu Ser Asp Arg Leu Asn Gln Val Leu Arg Trp			
805	810	815	
Ala Leu Gly Ser Val Glu Ile Leu Leu Ser Arg His Cys Pro Ile Trp			
820	825	830	
Tyr Gly Tyr Asn Gly Arg Leu Lys Leu Leu Glu Arg Leu Ala Tyr Ile			
835	840	845	
Asn Thr Ile Val Tyr Pro Ile Thr Ser Ile Pro Leu Ile Ala Tyr Cys			
850	855	860	
Val Leu Pro Ala Ile Cys Leu Leu Thr Asn Lys Phe Ile Ile Pro Glu			
865	870	875	880
Ile Ser Asn Tyr Ala Gly Met Phe Phe Ile Leu Leu Phe Ala Ser Ile			
885	890	895	
Phe Ala Thr Gly Ile Leu Glu Leu Arg Trp Ser Gly Val Gly Ile Glu			
900	905	910	
Asp Trp Trp Arg Asn Glu Gln Phe Trp Val Ile Gly Gly Thr Ser Ala			
915	920	925	
His Leu Phe Ala Val Phe Gln Gly Leu Leu Lys Val Leu Ala Gly Ile			

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930	935	940
Asp Thr Asn Phe Thr Val Thr Ser Lys Ala Ser Asp Glu Asp Gly Asp		
945	950	955
Phe Ala Glu Leu Tyr Val Phe Lys Trp Thr Ser Leu Leu Ile Pro Pro		960
965	970	975
Thr Thr Val Leu Val Ile Asn Leu Val Gly Met Val Ala Gly Ile Ser		
980	985	990
Tyr Ala Ile Asn Ser Gly Tyr Gln Ser Trp Gly Pro Leu Phe Gly Lys		
995	1000	1005
Leu Phe Phe Ser Ile Trp Val Ile Leu His Leu Tyr Pro Phe Leu Lys		
1010	1015	1020
Gly Leu Met Gly Arg Gln Asn Arg Thr Pro Thr Ile Val Ile Val Trp		
1025	1030	1035
Ser Ile Leu Leu Ala Ser Ile Phe Ser Leu Leu Trp Val Lys Ile Asp		1040
1045	1050	1055
Pro Phe Ile Ser Pro Thr Gln Lys Ala Ala Ala Leu Gly Gln Cys Gly		
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Val Asn Cys		
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cggccggcact cgggaggggaa agccgaggaa tgccgtgagt cggccgggggt ccggcgtttg	240
tgaactcgtg gagggctcgg attggtgccgc c atg gac ggc ggc gac gcc acg	292
Met Asp Gly Gly Asp Ala Thr	
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aat tcg ggg aag cat gtg gcc ggg cag gtg tgc cag atc tgc ggc gac	340
Asn Ser Gly Lys His Val Ala Gly Gln Val Cys Gln Ile Cys Gly Asp	

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10 15 20

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25 30 35	
tgc ggc ttc ccc gtg tgc cgc cca tgc tac gag tac gag cgc aag gac Cys Gly Phe Pro Val Cys Arg Pro Cys Tyr Glu Tyr Glu Arg Lys Asp	436
40 45 50 55	
ggc acc cag gcg tgc ccc cag tgc aag act aag tac aag cgc cac aaa Gly Thr Gln Ala Cys Pro Gln Cys Lys Thr Lys Tyr Lys Arg His Lys	484
60 65 70	
ggg agc cca cca gta cac ggt gag gaa aat gag gat gtg gat gct gac Gly Ser Pro Pro Val His Gly Glu Glu Asn Glu Asp Val Asp Ala Asp	532
75 80 85	
gat gtg agt gac tac aac tac caa gca tct ggc aac cag gat cag aag Asp Val Ser Asp Tyr Asn Tyr Gln Ala Ser Gly Asn Gln Asp Gln Lys	580
90 95 100	
caa aag att gct gag aga atg ctc act tgg cgg aca aac tca cgt ggc Gln Lys Ile Ala Glu Arg Met Leu Thr Trp Arg Thr Asn Ser Arg Gly	628
105 110 115	
agt gat att ggc ctg gct aag tat gac agc ggt gaa att ggg cat ggg Ser Asp Ile Gly Leu Ala Lys Tyr Asp Ser Gly Glu Ile Gly His Gly	676
120 125 130 135	
aag tat gac agt ggt gag atc cct cgt gga tat atc ccg tca cta act Lys Tyr Asp Ser Gly Glu Ile Pro Arg Gly Tyr Ile Pro Ser Leu Thr	724
140 145 150	
cat agc cag atc tca gga gag att cct gga gct tcc cct gat cat atg His Ser Gln Ile Ser Gly Glu Ile Pro Gly Ala Ser Pro Asp His Met	772
155 160 165	
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170 175 180	
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185 190 195	
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200 205 210 215	
ggt gca att cct atg acc aat gga aca agc att gct cca tca gaa ggg Gly Ala Ile Pro Met Thr Asn Gly Thr Ser Ile Ala Pro Ser Glu Gly	964
220 225 230	
cgt gga gtt gct gat att gat gct tct act gat tat aac atg gaa gat Arg Gly Val Ala Asp Ile Asp Ala Ser Thr Asp Tyr Asn Met Glu Asp	1012
235 240 245	

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att cct tca tcc aga ata aat ccg tac aga atg gtc att gtg cta cgt Ile Pro Ser Ser Arg Ile Asn Pro Tyr Arg Met Val Ile Val Leu Arg 265 270 275	1108
ttg gct gtt cta tgc ata ttc ttg cgc tac cgt atc aca cat cct gtg Leu Ala Val Leu Cys Ile Phe Leu Arg Tyr Arg Ile Thr His Pro Val 280 285 290 295	1156
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aac cgt gaa aca tac ctt gat aga ctg gct tta agg tat gac cga gaa Asn Arg Glu Thr Tyr Leu Asp Arg Leu Ala Leu Arg Tyr Asp Arg Glu 330 335 340	1300
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atc ctt gct gtc gat tat ccg gtt gac aag gta tct tgc tat gtt tcg Ile Leu Ala Val Asp Tyr Pro Val Asp Lys Val Ser Cys Tyr Val Ser 380 385 390	1444
gat gat gga gct gct atg ctg act ttt gat gct ctc tct gaa act tca Asp Asp Gly Ala Ala Met Leu Thr Phe Asp Ala Leu Ser Glu Thr Ser 395 400 405	1492
gag ttt gct aga aaa tgg gtt ccg ttc tgt aag aag tac aac ata gag Glu Phe Ala Arg Lys Trp Val Pro Phe Cys Lys Lys Tyr Asn Ile Glu 410 415 420	1540
cct ang gcc ccg gaa tgg tac ttt gct cag aaa att gat tac ttg aaa Pro Xaa Ala Pro Glu Trp Tyr Phe Ala Gln Lys Ile Asp Tyr Leu Lys 425 430 435	1588
gac aaa gtt caa acc tca ttt gtg aaa gaa cgc cgg gcc atg aag aga Asp Lys Val Gln Thr Ser Phe Val Lys Glu Arg Arg Ala Met Lys Arg 440 445 450 455	1636
gaa tat gaa gaa ttc aaa gtt cgt atc aat ggt ctt gta gcc aag gca Glu Tyr Glu Glu Phe Lys Val Arg Ile Asn Gly Leu Val Ala Lys Ala 460 465 470	1684
caa aaa gtt ccc gag gag gga tgg atc atg caa gat ggt aca cct tgg Gln Lys Val Pro Glu Glu Gly Trp Ile Met Gln Asp Gly Thr Pro Trp	1732

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475	480	485	
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acg tca aaa tct aag aag agc tcg gaa aag aag tca cat aga cac Thr Ser Lys Ser Lys Ser Ser Glu Lys Lys Ser His Arg His 665	670	675	2308
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cag aac cgcc acg ccg acc att gtc gtt gtc tgg gct atc ctc ctt gcg Gln Asn Arg Thr Pro Thr Ile Val Val Val Trp Ala Ile Leu Leu Ala 1035 1040 1045	3412
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195	200	205
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Thr Asp Tyr Asn Met Glu Asp Ala Leu Leu Asn Asp Glu Thr Arg Gln		
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340	345	350
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Lys Val Ser Cys Tyr Val Ser Asp Asp Gly Ala Ala Met Leu Thr Phe		
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119

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data: 60/096,822 17 August 1998 (17.08.98) US	
(71) Applicant (<i>for all designated States except US</i>): PIONEER HI-BRED INTERNATIONAL, INC. [US/US]; 800 Capital Square, 400 Locust Street, Des Moines, IA 50309 (US).	
(72) Inventors; and	
(75) Inventors/Applicants (<i>for US only</i>): DHUGGA, Kanwarpal, S. [US/US]; 8320 Barnham Drive, Johnston, IA 50131 (US). HELENTJARIS, Timothy, G. [US/US]; 2960 N.W. 73rd Lane, Ankeny, IA 50021 (US). BOWEN, Benjamin, A. [GB/US]; 7027 Buckingham Boulevard, Berkeley, CA 94705 (US). WANG, Xun [CN/US]; 12524 Caminito Vista Soledad, San Diego, CA 92130 (US).	
(74) Agents: BLAIR, Debra, L. et al.; 7100 N.W. 62nd Avenue, Darwin Building, Johnston, IA 50131-1000 (US).	

(54) Title: MAIZE CELLULOSE SYNTHASES AND USES THEREOF

(57) Abstract

The invention provides isolated cellulose synthase nucleic acids and their encoded proteins. The present invention provides methods and compositions relating to altering cellulose synthase concentration and/or composition of plants. The invention further provides recombinant expression cassettes, host cells, and transgenic plants.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/18760

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N15/54 C12N9/10 C12N5/10 C12N15/82

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
1 X	WO 98 00549 A (WILLIAMSON RICHARD EDWARD ;PENG LIANGCAI (AU); ARIOLI ANTONIO (AU)) 8 January 1998 (1998-01-08) abstract page 4, line 10 - line 14 page 7, line 19 - line 29 page 8, line 16 - line 21 page 11, line 6 - line 12 page 17, line 4 - line 19 page 24, line 15 - line 18 page 28, line 15 - line 21 --- page 4, line 10 - line 14 page 7, line 19 - line 29 page 8, line 16 - line 21 page 11, line 6 - line 12 page 17, line 4 - line 19 page 24, line 15 - line 18 page 28, line 15 - line 21	1-15
1 A	WO 98 18949 A (CALGENE INC ;PEAR JULIE R (US); STALKER DAVID M (US); DELMER DEBOR) 7 May 1998 (1998-05-07) cited in the application abstract page 7, line 14 -page 9, line 25 --- --- -/-/	1-15

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Patent family members are listed in annex.

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Date of the actual completion of the international search

22 June 2000

Date of mailing of the international search report

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Ceder, O

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/18760

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARIOLI ET AL.: "Molecular analysis of cellulose biosynthesis in <i>Arabidopsis</i> " EMBL SEQUENCE DATABASE, 1 June 1998 (1998-06-01), XP002125688 HEIDELBERG DE Ac 048947 the whole document -& ARIOLI ET AL.: "Molecular analysis of cellulose biosynthesis in <i>Arabidopsis</i> " EMBL SEQUENCE DATABASE, 3 February 1998 (1998-02-03), XP002125689 HEIDELBERG DE AC AF027174 the whole document -& ARIOLI ET AL.: "Molecular analysis of cellulose biosynthesis in <i>Arabidopsis</i> " EMBL SEQUENCE DATABASE, 1 June 1998 (1998-06-01), XP002140697 HEIDELBERG DE Ac 048948 the whole document -& ARIOLI ET AL.: "Molecular analysis of cellulose biosynthesis in <i>Arabidopsis</i> " EMBL SEQUENCE DATABASE, 20 January 1998 (1998-01-20), XP002140698 HEIDELBERG DE Ac AF030052 the whole document -& ARIOLI ET AL.: "Molecular analysis of cellulose biosynthesis in <i>Arabidopsis</i> " EMBL SEQUENCE DATABASE, 1 June 1998 (1998-06-01), XP002140699 HEIDELBERG DE Ac 048946 the whole document -& ARIOLI ET AL.: "Molecular analysis of cellulose biosynthesis in <i>Arabidopsis</i> " EMBL SEQUENCE DATABASE, 3 February 1998 (1998-02-03), XP002140700 HEIDELBERG DE Ac AF027173 the whole document -& ARIOLI ET AL.: "Molecular analysis of cellulose biosynthesis in <i>Arabidopsis</i> " SCIENCE, vol. 279, no. 5351, 30 January 1998 (1998-01-30), pages 717-720, XP002124283 abstract; figure 3	15
A	---	1
X	---	15
X	---	1
X	---	15
X	---	15
A	---	15
X	---	15
A	---	1

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WU ET AL.: "Cellulose synthase" EMBL SEQUENCE DATABASE, 1 August 1998 (1998-08-01), XP002140701 HEIDELBERG DE Ac 065338 the whole document --- PEAR J R ET AL: "HIGHER PLANTS CONTAIN HOMOLOGS OF THE BACTERIAL CELA GENES ENCODINGTHE CATALYTIC SUBUNIT OF CELLULOSE SYNTHASE" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 93, page 12637-12642 XP002061424 ISSN: 0027-8424 --- AMOR Y ET AL: "EVIDENCE FOR A CYCLIC DIGUANYLIC ACID-DEPENDENT CELLULOSE SYNTHASE IN PLANTS" PLANT CELL,US,AMERICAN SOCIETY OF PLANT PHYSIOLOGISTS, ROCKVILLE, MD, vol. 3, page 989-995 XP002061420 ISSN: 1040-4651 --- US 5 723 764 A (SINGLETARY GEORGE WILLIAM ET AL) 3 March 1998 (1998-03-03) abstract; claims --- WO 00 04166 A (THORPE ET AL.) 27 January 2000 (2000-01-27) abstract; claims -----	15
E		2-12
		1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/18760

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-15 all partly (inventions 1,2,3,4,5,7 and 15 searched)

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: 1-15 all partial

An isolated nucleic acid selected from the groups as defined in claim 1 and uses of said nucleic acid, and a protein selected from the groups as defined in claim 15, where the nucleic acid sequence is SEQ ID NO 1 and the protein sequence is SEQ ID NO 2.

2. Claims: Inventions 2-15: Claims 1-15 all partial

Idem as subject 1 but limited to each of the nucleic acid sequences as in SEQ ID NOS 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57 and corresponding protein sequences SEQ ID NOS 6, 10, 14, 18, 22, 26, 30, 34, 42, 46, 50, 54, and 58, where invention 2 is limited to SEQ ID NOS 5 and 6, invention 3 is limited to SEQ ID NOS 9 and 10, , invention 15 is limited to SEQ ID NOS 57 and 58.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/18760

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9800549	A 08-01-1998	AU CA EP	3160397 A 2259126 A 0956353 A		21-01-1998 08-01-1998 17-11-1999
WO 9818949	A 07-05-1998	AU BR EP	5092398 A 9712457 A 0938573 A		22-05-1998 19-10-1999 01-09-1999
US 5723764	A 03-03-1998		NONE		
WO 0004166	A 27-01-2000	AU	5100199 A		07-02-2000